Liza M. Walsh
Christine I. Gannon
Katelyn O'Reilly
William T. Walsh, Jr.
WALSH PIZZI O'REILLY FALANGA LLP
One Riverfront Plaza
1037 Raymond Blvd, Suite 600
Newark, NJ 07102
(973) 757-1101

Attorneys for Plaintiffs Sanofi-Aventis U.S. LLC, Sanofi-Aventis Deutschland GmbH, and Sanofi Winthrop Industrie

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SANOFI-AVENTIS U.S. LLC, SANOFI-AVENTIS DEUTSCHLAND GMBH, and SANOFI WINTHROP INDUSTRIE, Plaintiffs, v. MYLAN GMBH, BIOCON LTD., BIOCON RESEARCH LTD., BIOCON SDN. BHD., and BIOCON S.A. Defendants.	Civil Action No. 2:17-cv-09105-SRC-CLW

DECLARATION OF LIZA M. WALSH IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT, OR , IN THE ALTERNATIVE MOTION IN LIMINE

I, Liza M. Walsh, hereby declare as follows:

1. I am a partner of Walsh Pizzi O'Reilly Falanga LLP, counsel for Plaintiffs Sanofi-Aventis U.S. LLC, Sanofi-Aventis Deutschland GmbH, and Sanofi Winthrop Industrie ("Plaintiffs" or "Sanofi") in the above-captioned action.

2. I am a member in good standing of the Bar of New Jersey.

3. I submit this declaration on behalf of Plaintiffs and in support of Plaintiffs' Motion for Summary Judgment, or, in the alternative, Motion *in Limine*.

4. Attached hereto as Exhibit 1 is a true and correct copy of *In re Certain Hybrid Electric Vehicles and Components Thereof*, Inv. No. 337-TA-1042, Order No. 30 (Initial Determination) (USITC Nov. 2, 2017).

5. Attached hereto as Exhibit 2 is a true and correct copy of the *Invited Brief for the Director U.S. Patent and Trademark Office as Amicus Curiae in Support of Neither Party*, filed in *BTG Int'l Ltd. v. Amneal Pharm. LLC*, No. 2019-1147, Docket No. 123 (Fed. Cir. Feb. 1, 2019).

6. Attached hereto as Exhibit 3 is a true and correct copy of Mylan Pharmaceuticals Inc.'s petition for *inter partes* review IPR No. 2017-01526 (the "IPR"), challenging claims 1-25 of U.S. Patent No. 7,476,652 (the "'652 patent"), filed on June 5, 2017 before the Patent Trial and Appeal Board ("PTAB").

7. Attached hereto as Exhibit 4 is a true and correct copy of the PTAB's December 13, 2017 decision instituting *inter partes* review of Mylan Pharmaceuticals Inc.'s IPR challenging claims 1-25 of the '652 patent.

8. Attached hereto as Exhibit 5 is a true and correct copy of PTAB's December 12, 2018 final written decision in the IPR pursuant to 35 U.S.C. § 318(a).

9. Attached hereto as Exhibit 6 is a true and correct copy of a printout of the docket, as of November 7, 2019, for *Sanofi-Aventis Deutschland GmbH v. Mylan Pharmaceuticals Inc.*, No. 19-1368 (Fed. Cir.).

10. Attached hereto as Exhibit 7 is a true and correct copy of the Lantus Label published in the 55th Edition of the Physician's Desk Reference, produced in this litigation as MYL_IG00989950- MYL_IG00989954.

I declare under penalty of perjury that the foregoing is true and correct.

WALSH PIZZI O'REILLY FALANGA LLP

Dated: November 8, 2019

s/ Liza M. Walsh
Liza M. Walsh

EXHIBIT 1

UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C.

In the Matter of	
CERTAIN HYBRID ELECTRIC VEHICLES AND COMPONENTS THEREOF	**Inv. No. 337-TA-1042**

Order No. 30 (Initial Determination)

On August 31, 2017, pursuant to 19 C.F.R. § 210.18, complainants Paice LLC and Abell Foundation, Inc. (collectively, "Paice") filed a motion for summary determination that respondent Ford Motor Company ("Ford") is estopped from challenging validity of claims for which the Patent Trial and Appeal Board ("PTAB") has rendered a final written decision under 35 U.S.C. § 315(e). Motion Docket No. 1042-34. On September 11, 2017, Ford filed a response in opposition.

On September 22, 2017, Paice filed a motion for leave to file a reply, and a reply. Motion Docket No. 1042-43. On October 16, 2017, Ford filed a motion for leave to file a sur-reply, and a sur-reply. Motion Docket No. 1042-51. The parties' motions for leave are granted.

Paice argues:

> Complainants respectfully request the ALJ estop Ford from asserting in this Investigation invalidity grounds that it raised or reasonably could have raised in its *inter partes* review petitions before the Patent Trial and Review Board (PTAB). The IPR estoppel provision (35 U.S.C. § 315(e)) prevents IPR petitioners from taking a second bite at the apple on invalidity once the PTAB issues a final written decision. Ford, however, seeks just that—a second attempt to challenge the validity of claims that have been fully litigated at the PTAB. Win or lose, Ford should be held to the invalidity grounds it presented to the PTAB. 35 U.S.C. § 315(e) is unequivocal on this point. Because there is no factual dispute that 35 U.S.C. § 315(e) prevents Ford from re-litigating invalidity at the ITC, this issue is appropriate for summary determination.

Mem. at 1.

In its opposition, Ford argues:

> Complainants Paice LLC and Abell Foundation, Inc. (collectively, "Paice") have advanced an unprecedented position: that Respondent Ford Motor Company ("Ford") is estopped from here defending itself against infringement charges by showing that asserted patent claims are unpatentable where ***those claims were already held unpatentable*** by the Patent Trial and Appeal Board ("PTAB"). Paice's motion is inconsistent with the plain language of 35 U.S.C. § 315(e)(2) which is explicitly directed to "estoppel" – and the Supreme Court defines estoppel as preventing a party from relitigating an issue ***previously lost***. Courts do not apply estoppel to a ***successful*** litigant advancing the same position. Paice did not cite any cases in which a petitioner was estopped under § 315(e)(2) from proving invalidity after ***successfully*** having done so.
>
> This is just one more cog in Paice's attempt to game the system to assert patents despite the PTAB having held 272 patent claims unpatentable. With little left apart from narrow claims, and where even its broader affirmed unpatentable claims were directed to torque control strategies utterly different from Ford's control strategies, Paice turned its sights on pressuring Ford through the ITC with the hope that the ITC will outpace the appeal process. The Federal Circuit, however, has reached decision on eight appeals of the unpatentable claims. The unpatentability of all claims have thus far been affirmed except ***one claim*** where the PTAB decision was ***vacated and remanded***; the last subset of unpatentable claims are briefed and ready for oral argument. If the Federal Circuit again affirms, the patent claims will be nullified. But, if the Federal Circuit vacates and remands, then the ITC will ***need to rely on its own decision on validity***. Thus, Paice's estoppel motion is premature because an evaluation of estoppel should be part of the Initial Determination, ***together with a reasoned decision on validity***. While asserting invalid patent claims here, Paice is remarkably attempting to prevent Ford from presenting evidence of that invalidity to the Commission. Respectfully, Paice's perversion of judicial process should be rejected and its motion denied.

Opp'n at 1-2 (emphasis in original).

The Commission Rules provide that "[a]ny party may move with any necessary supporting affidavits for a summary determination in its favor upon all or part of the issues to be determined in the investigation." 19 C.F.R. § 210.18(a). Summary determination "shall be rendered if pleadings and any depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a summary determination as a matter of law." 19 C.F.R.

§ 210.18(b).

Background

In 2014, Ford filed 25 *inter partes* review petitions on Paice's patents, including the four patents asserted in this Investigation. Ford's IPR petitions relate to claims that Paice asserts in this investigation or rely on for domestic industry. These claims are claims 24 and 28 of the '347 patent; claim 3 of the '388 patent; and claims 25, 240, 278, 290, and 292 of the '634 patent. For each of these claims, the PTAB issued a final written decision as set forth below:

Asserted Claim	IPR No.	Ground(s)	PTAB finding in Final Written Decision	Current Status
Claim 3, '388 patent	IPR2014-00875	(1) Ehsani[1] and Vittone[2] and (2) Kawakatsu[3] and Vittone	Found invalid (Ex. 1, IPR2014-00875, Final Written Decision (Nov. 23, 2015))	Federal Circuit vacated and remanded
Claim 24, '347 patent	IPR2014-00884	Tabata '201[4] and Tabata '541[5]	Found valid (Ex. 2, IPR2014-00884, Final Written Decision (Dec. 10, 2015))	Valid
Claim 28, '347 patent	IPR2015-00794	Ibaraki '882[6]	Found invalid (Ex. 3, IPR2015-00794, Final Written Decision (Nov. 1, 2016))	Appealed to Federal Circuit – decision pending
Claim 25, '634 patent	IPR2015-00790	Ibaraki '882 and Kawakatsu	Found invalid (Ex. 4, IPR201500790, Final Written Decision (Nov. 4, 2016))	Appealed to Federal Circuit – decision

[1] U.S. Patent No. 5,586,613.

[2] Oreste Vittone et al., FIAT Research Centre, *Fiat Conceptual Approach to Hybrid Car Design*, 12th International Electric Vehicle Symposium (1994).

[3] U.S. Patent No. 4,335,429.

[4] U.S. Patent No. 5,841,201.

[5] U.S. Patent No. 6,158,541.

[6] U.S. Patent No. 5,789,882.

				pending
Claim 240, '634 patent	IPR2015-00722	Ibaraki '882 and Suga[7]	Found invalid (Ex. 5, IPR2015-00722, Final Written Decision (Sept. 26, 2016))	Appealed to Federal Circuit – decision pending
Claim 278, '634 patent	IPR2015-00801	Severinsky '970[8] and Yamaguchi[9]	Found invalid (Ex. 6, IPR2015-00801, Final Written Decision (Oct. 21, 2016))	Appealed to Federal Circuit – decision pending
Claim 290, '634 patent	IPR2015-00801	Severinsky '970 and Yamaguchi	Found invalid (Ex. 6, IPR2015-00801, Final Written Decision (Oct. 21, 2016))	Appealed to Federal Circuit – decision pending
Claim 292, '634 patent	IPR2015-00606	Severinsky '970 and the '455 PCT Publication[10]	Found invalid (Ex. 7, IPR2015-00606, Final Written Decision (Nov. 8, 2016))	Appealed to Federal Circuit – decision pending

See Mem. at 1-2.

In other circumstances, Paice has withdrawn claims upon final adjudication at the Federal Circuit. *See* Notice of Commission Decision Not to Review an Initial Determination Granting a Motion to Terminate the Investigation as to One Asserted Patent, and Certain Claims of Three Additional Patents (June 26, 2017). With respect to the claims on appeal at the Federal Circuit, briefing has been completed and the parties are in the midst of scheduling oral arguments.

Discussion

35 U.S.C. § 315(e)(2) provides:

Civil actions and other proceedings.—

[7] U.S. Patent No. 5,623,104.

[8] U.S. Patent No. 5,343,970.

[9] U.S. Patent No. 5,865,263.

[10] PCT application, published as WO00/15455.

> The petitioner in an *inter partes* review of a claim in a patent under this chapter that results in a final written decision under section 318(a), or the real party in interest or privy of the petitioner, may not assert either in a civil action arising in whole or in part under section 1338 of title 28 or in a proceeding before the International Trade Commission under section 337 of the Tariff Act of 1930 that the claim is invalid on any ground that the petitioner raised or reasonably could have raised during that *inter partes* review.

When enacting the America Invents Act, Congress intended to apply "a strengthened estoppel standard to prevent petitioners from raising in a subsequent challenge the same patent issues that were raised or reasonably could have been raised in the prior challenge." 157 Cong. Rec. S952 (daily ed. Feb. 28, 2011) (statement of Sen. Grassley). The legislative history does not require that the petitioner must be unsuccessful in its challenge for this strengthened estoppel provision to apply. Instead, Congress's focus concerned a provision that would "significantly reduce the ability to use post-grant procedures for abusive serial challenges to patents." *Id.* Indeed, Congress recognized that repeated litigation and administrative attacks on the validity of a patent "would frustrate the purpose of the [post-grant] section as providing quick and cost effective alternatives to litigation." H.R. Rep. No. 112-98 at 48 (2011).

Based on the plain language of the statute, and its interpretation by courts, it is clear that estoppel applies to invalidity challenges based on grounds that the petitioner raised in its IPR petition. Yet, while some courts have also interpreted the statutory estoppel to apply to grounds that could have been raised in the petition, others have held that the estoppel cannot apply to grounds that were absent from the petition (*i.e.*, inasmuch as the estoppel should be focused only on events "during" the *inter partes* review). *See Cobalt Boats, LLC v. Sea Ray Boats, Inc.*, No. 2:15cv21, 2017 WL 2605977, at *3 (E.D. Va. June 5, 2017) (discussing the "split in the district courts"); *see also Douglas Dynamics. LLC v. Mever Prod. LLC*, No. 14cv886, 2017 WL 1382556, at *4 (W.D. Wis. Apr. 18, 2017), *reconsideration granted in part*, No. 14cv886, 2017

WL 2116714 (W.D. Wis. May 15, 2017) (not changing the analysis regarding scope of estoppel) ("[T]he court will construe the statutory language 'any ground that the petitioner . . . reasonably could have raised during that inter partes review' to include non-petitioned grounds that the defendant chose not to present in its petition to PTAB."); *Intellectual Ventures I LLC v. Toshiba Corp.*, No. 13-453-SLR, 221 F. Supp. 3d 534, 553-54 (D. Del. 2016) (citing *Shaw Indus. Grp., Inc. v. Automated Creel Sys., Inc.*, 817 F.3d 1293 (Fed. Cir. 2016)).

Same Invalidity Grounds Ford Raised in the IPRs

A ground for invalidity petitioned on, instituted on, and subject to a final written decision by the PTAB cannot be asserted again before the ITC. *See* 35 U.S.C. § 315(e); *Intellectual Ventures I*, 221 F. Supp. 3d at 553-54; *Evolutionary Intelligence, LLC v. Sprint Nextel Corp.*, No. C-13-4513-RMW, 2014 WL 819277, at *5 (N.D. Cal. Feb. 28, 2014) ("IPR petitioners are subject to statutory estoppel provisions preventing them from relitigating invalidity arguments that were raised or could have been raised in the IPR").

Ford challenges the validity of claim 3 of the '388 patent and claims 25, 278, and 290 of the '634 patent using the exact same grounds for invalidity in its expert report[11] as shown below:

Asserted Claim	IPR Ground(s)	Invalidity Grounds in Expert Report
Claim 3, '388 patent	(1) Ehsani and Vittone and (2) Kawakatsu and Vittone	(1) Ehsani and Vittone (Stein Rpt. at 330-362) and (2) Kawakatsu and Vittone (Stein Rpt. at 362-394)
Claim 25, '634 patent	Ibaraki '882 and Kawakatsu	Ibaraki '882 and Kawakatsu (Davis Rpt. at 490-493)
Claim 278, '634	Severinsky '970 and	Severinsky '970 and Yamaguchi (Stein

[11] *See* EDIS Doc. ID No. 621059, Expert Report of Dr. Jeffrey L. Stein ("Stein Rpt."); EDIS Doc. ID No. 621037, Expert Report of Dr. Gregory W. Davis ("Davis Rpt.").

patent	Yamaguchi	Rpt. at 593-622)
Claim 290, '634 patent	Severinsky '970 and Yamaguchi	Severinsky '970 and Yamaguchi (Stein Rpt. at 593-620, 622-629)

See Mem. at 5-6.

As an initial matter, as noted above, PTAB's final written decision regarding claim 3 of the '388 patent has been vacated and remanded by the Federal Circuit. The Supreme Court recognized in *United States v. Munsingwear, Inc.*, 340 U.S. 36, 39-40 (1950) that vacating a judgment prevents a judgment "from spawning any legal consequences." Thus, the estoppel provision of 35 U.S.C. § 315(e) cannot apply to claim 3 inasmuch as there is no longer a "final written decision." *See Shaw Indus. Grp.*, 817 F.3d at 1297 (Federal Circuit has "jurisdiction to review the Board's final written decisions in IPRs").

Thus, with the exception of claim 3 of the '388 patent, Ford has challenged each of the claims above on the same invalidity grounds (*i.e.*, the same combinations of art) raised before the PTAB, and they are now the subject of a final written PTAB decision. Consequently, the pending motion is granted with respect to claims 25, 278, and 290 of the '634 patent.[12]

[12] Ford raises an issue with respect to the fact that it prevailed before the PTAB. That issue goes more to the weight or effect to be accorded a PTAB decision, rather than to the estoppel which is based on the statute that prevents the same grounds from being litigated before the PTAB, and then later in the district courts or at the Commission. The question of the effect of a PTAB final written decision is also a new issue at the Commission. *See, e.g.*, *Certain Foam Footwear*, Inv. No. 337-TA-567, Commission Order Denying Petition to Modify, Suspend, or Rescind the Commission's General Exclusion Order and Cease and Desist Order with Respect to U.S. Patent No. D517,789 (and case cited therein) (Oct. 20, 2017); *Certain Three-Dimensional Cinema Systems and Components Thereof*, Inv. No. 337-TA-939, Final Determination Finding a Violation of Section 337; Issuance of a Limited Exclusion Order and Cease and Desist Orders; Termination of the Investigation (July 21, 2016). Indeed, Congress intended to apply "a strengthened estoppel standard to prevent petitioners from raising in a subsequent challenge the same patent issues that were raised or reasonably could have been raised in the prior challenge." 157 Cong. Rec. S952 (daily ed. Feb. 28, 2011) (statement of Sen. Grassley). The legislative history does not require that the petitioner must be unsuccessful in its challenge for this strengthened estoppel provision to apply. Congress recognized that repeated litigation and

Invalidity Grounds Ford Reasonably Could Have Raised During the IPRs

Estoppel also applies to invalidity grounds that Ford reasonably could have raised during its IPR proceedings. *See* 35 U.S.C. § 315(e); *see also* Mem. Ex. 10, *Evolutionary Intelligence, LLC*, 2014 WL 819277, at *5. In its expert reports, Ford reasserts its invalidity grounds from the IPRs and relies on new combinations of known references that Ford has used in its various IPRs. A summary of Ford's invalidity challenges is provided below:

Asserted Claim	IPR Ground(s)	Invalidity Grounds in Expert Report
Claim 28, '347 patent	Ibaraki '882	(1) Ibaraki '882 (Davis Rpt. at 258-327); (2) Severinsky '970 (Davis Rpt. at 76-138); and (3) Bumby References[13] (Davis Rpt. at 199-255)
Claim 240, '634 patent	Ibaraki '882 and Suga	(1) Ibaraki '882 and Suga (Davis Rpt. at 587-92); and (2) Seversinky '970 and Suga (Stein Rpt. at 584-93)
Claim 292, '634 patent	Severinsky '970 and '455 PCT Publication	(1) Severinsky '970 and '455 PCT Publication (Stein Rpt. at 404-25); and (2) Severinsky '970 and SAE 1996[14] (Stein Rpt. at 425-54)

See Mem. at 7.

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administrative attacks on the validity of a patent "would frustrate the purpose of the [post-grant] section as providing quick and cost effective alternatives to litigation." H.R. Rep. No. 112-98 at 48 (2011).

[13] Ford defines the "Bumby References" as the following publications: J.R. Bumby et al., *Computer Modelling of the Automotive Energy Requirements for Internal Combustion Engine and Battery Electric-powered Vehicles*, IEE PROC., vol. 132, pt. A (Sept. 1985) ("Bumby I"); J.R. Bumby et al., *Optimisation and Control of a Hybrid Electric Car*, IEE PROC., vol. 134, pt. D (Nov. 1987) ("Bumby II"); I. Forster and J.R. Bumby, *A Hybrid Internal Combustion Engine/Battery Electric Passenger Car for Petroleum Displacement*, PROC. INST. MECH. ENGRS., vol. 202, no. D1 (Jan. 1998) ("Bumby III"); J.R. Bumby and P.W. Masding, *A Test-Bed Facility for Hybrid IC Engine-Battery Electric Road Vehicle Drive Trains*, TRANS. INST. MEAS. & CONT., vol. 10, no. 2 (Apr. 1988) ("Bumby IV"); P.W. Masding and J.R. Bumby, *Integrated Microprocessor Control of a Hybrid I.C. Engine/Battery-electric Automotive Power Train*, TRANS. INST. MEAS. & CONT., vol. 10, no. 2 (Jan. 1990) ("Bumby V").

[14] 1996 Society of Automotive Engineers (SAE) Special Publication SP-1156.

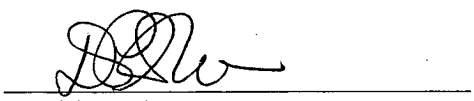
Paice argues that inasmuch as "Ford actually knew of each of the references identified above, there is no question that Ford should be estopped from asserting these grounds at the ITC." Mem. at 8. Indeed, even though Ford knew of the references, it did not petition on the combinations at issue, or otherwise raise them during IPR proceedings. It remains unclear whether Ford reasonably could have raised these new combinations of known references in its IPR petition or during the *inter partes* review proceedings. An examination of the pending motion and related filings shows a paucity of details that would make it clear that those combinations reasonably could have been raised. Thus, even taking an approach to estoppel that would apply estoppel in connection with grounds not raised in the petition, the pending motion is denied because there remain genuine issues of material fact, and it has not been shown that Paice is entitled to summary determination as a matter of law.

* * *

Accordingly, it is the initial determination of the administrative law judge that Motion No. 1042-34 is granted in part.[15]

[15] Inasmuch as this initial determination will be pending during the evidentiary hearing, and the estoppel issue presented to the Commission may be a matter of first impression, Ford will not be prevented from offering the entirety of its invalidity case during the hearing (provided it is otherwise proper), and Paice may cross-examine if desired.

Pursuant to 19 C.F.R. § 210.42(h), this initial determination shall become the determination of the Commission unless a party files a petition for review of the initial determination pursuant to 19 C.F.R. § 210.43(a), or the Commission, pursuant to19 C.F.R. § 210.44, orders on its own motion a review of the initial determination or certain issues contained herein.



David P. Shaw
Administrative Law Judge

Issued: November 1, 2017

CERTAIN HYBRID ELECTRIC VEHICLES AND COMPONENTS THEREOF

INV. NO. 337-TA-1042

PUBLIC CERTIFICATE OF SERVICE

I, Lisa R. Barton, hereby certify that the attached **Order No. 30** has been served upon the following parties as indicated, on NOV 02 2017.

Lisa R. Barton, Secretary
U.S. International Trade Commission
500 E Street SW, Room 112A
Washington, DC 20436

FOR COMPLAINANTS PAICE LLC; AND ABELL FOUNDATION, INC.:	
Brian J. Livedalen, Esq. **FISH & RICHARDSON P.C.** 901 15th Street, NW 7th Floor Washington, DC 20005	( ) Via Hand Delivery (✓) Express Delivery ( ) Via First Class Mail ( ) Other: _____
FOR RESPONDENT FORD MOTOR COMPANY:	
Jamie D. Underwood, Esq. **ALSTON & BIRD LLP** 950 F Street NW Washington, DC 20004	( ) Via Hand Delivery (✓) Express Delivery ( ) Via First Class Mail ( ) Other: _____

EXHIBIT 2

2019-1147, -1148, -1323, -1324, -1325

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2019-1147

BTG INTERNATIONAL LIMITED, JANSSEN BIOTECH, INC., JANSSEN ONCOLOGY, INC., JANSSEN RESEARCH & DEVELOPMENT, LLC,
Plaintiffs-Appellants

v.

AMNEAL PHARMACEUTICALS LLC, AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., WOCKHARDT BIO AG, WOCKHARDT USA LLC, WOCKHARDT LTD., MYLAN PHARMACEUTICALS INC., MYLAN INC., WEST-WARD PHARMACEUTICALS CORP., NKA HIKMA PHARMACEUTICALS USA INC., HIKMA PHARMACEUTICALS LLC, TEVA PHARMACEUTICALS USA, INC.,
Defendants-Appellees

PAR PHARMACEUTICAL, INC., PAR PHARMACEUTICAL COMPANIES, INC., RISING PHARMACEUTICALS, INC.,
Defendants

Appeals from the United States District Court for the District of New Jersey in Nos. 2:15-cv-05909-KM-JBC, 2:16-cv-02449-KM-JBC, and 2:17-cv-06435-KM-JBC, Judge Kevin McNulty.

- -

(Caption continued on next page)

2019-1148

BTG INTERNATIONAL LIMITED, JANSSEN BIOTECH, INC., JANSSEN ONCOLOGY, INC., JANSSEN RESEARCH & DEVELOPMENT, LLC,
Plaintiffs-Appellants

v.

AMERIGEN PHARMACEUTICALS, INC., AMERIGEN PHARMACEUTICALS LIMITED,
Defendants-Appellees

Appeal from the United States District Court for the District of New Jersey in No. 2:16-cv-02449-KM-JBC, Judge Kevin McNulty.

- -

2019-1323

JANSSEN ONCOLOGY, INC.,
Appellant

v.

AMERIGEN PHARMACEUTICALS LIMITED, ARGENTUM PHARMACEUTICALS LLC,
Appellees

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00286 and IPR2016-01317.

- -

(Caption continued on next page)

2019-1324

JANSSEN ONCOLOGY, INC.,

Appellant

v.

MYLAN PHARMACEUTICALS INC., AMNEAL PHARMACEUTICALS LLC, AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., TEVA PHARMACEUTICALS USA, INC., WEST-WARD PHARMACEUTICAL CORPORATION, HIKMA PHARMACEUTICALS LLC,

Appellees

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-01332 and IPR2017-00853.

- -

2019-1325

JANSSEN ONCOLOGY, INC.,

Appellant

v.

WOCKHARDT BIO AG,

Appellee

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2016-01582.

INVITED BRIEF FOR THE DIRECTOR – U.S. PATENT AND TRADEMARK OFFICE AS AMICUS CURIAE IN SUPPORT OF NEITHER PARTY

JENNIFER L. UTRECHT
SCOTT R. MCINTOSH
MARK R. FREEMAN
Of Counsel

Attorneys, Appellate Staff
Civil Division
U.S. Department of Justice

THOMAS W. KRAUSE
Solicitor

FARHEENA Y. RASHEED
Senior Counsel for Patent Law & Litigation

FRANCES M. LYNCH
ROBERT J. MCMANUS
JOSEPH MATAL
Associate Solicitors

Attorneys for the Director of the U.S. Patent and Trademark Office

February 1, 2019

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Cases **Page(s)**

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STATEMENT OF INTEREST

The Director respectfully submits this amicus brief pursuant to Fed. R. App. P. 29(a) and this Court's Orders of November 20, 2018 (ECF No. 68), December 12, 2018 (ECF No. 83), and December 20, 2018 (ECF No. 86).

The Director's brief takes no position on the merits of this case.

SUMMARY

The Director of the U.S. Patent and Trademark Office submits this briefing in response to the Court's invitation dated November 20, 2018, ECF No. 68, requesting amicus participation by the USPTO on the following questions:

> 1. Whether a petitioner is estopped from challenging claims in district court under 35 U.S.C. § 315(e)(2) based on a ground that it brought in an inter partes review, which resulted in a final written decision holding the claims unpatentable but which has a pending request for rehearing.
>
> 2. Whether a decision is a "final written decision" under 35 U.S.C. § 315(e)(2) if the period for rehearing under 37 C.F.R. § 42.71(d) has not yet expired.
>
> 3. Whether a PTAB decision on the pending requests for rehearing could moot the estoppel issue.
>
> 4. Whether a district court can stay a case pending the outcome of a request for rehearing of a final written decision and/or appeal from a final written decision.

The first question has two parts: (a) whether "estoppel" under § 315(e)(2) attaches to a successful petitioner, and (b) whether the estoppel attaches (i) when the final written decision issues or (ii) only after any rehearing request has been addressed. The plain language of the statute answers both subparts, and its drafting history quiets any doubt. As to the successful-petitioner question, the plain language makes no distinction between successful and unsuccessful petitioners, in stark contrast to the statute's inter partes reexamination predecessor. Likewise, the plain language requires estoppel to attach when the proceedings result in a final

written decision, regardless of whether a rehearing request remains outstanding; this is again in contrast to the inter partes reexamination predecessor statute, which delays application of estoppel until all appeals have been exhausted. Moreover, the answer to the second subpart flows logically from the answer to the first—if the estoppel is not outcome dependent, then there is no need to wait beyond issuance of a final written decision to attach it.

The answer to the second question is not implicated under the facts of this case because BTG's rehearing petitions were timely filed before the district court trial on invalidity and were pending at the time of the district court's decision. If reached, the answer to the first question resolves this question as well: estoppel attaches regardless of whether a rehearing request remains outstanding.

As to the third question, estoppel attaches under section 315(e)(2) as soon as the proceedings result in a written decision as to the patentability of the challenged claims. That remains true even if a party petitions for rehearing. Accordingly, the Board's decision to deny the petitions for rehearing here did not affect the application of section 315(e)(2) to the district court proceedings.

As to question four, a district court has considerable discretion to stay proceedings under established case law and nothing in § 315(e)(2) limits that discretion.

DETAILED RESPONSE TO ORDER

As an initial matter, the USPTO notes that if the Court were to affirm the PTAB's findings of unpatentability in the proceedings below, it would not necessarily have to fully resolve the questions posed in the Court's order. *See* infra p. 17 n.6. Subject to that caveat, the USPTO's answers to the Court's questions are set forth below.

> ***(1) Whether a petitioner is estopped from challenging claims in district court under 35 U.S.C. § 315(e)(2) based on a ground that it brought in an inter partes review, which resulted in a final written decision holding the claims unpatentable but which has a pending request for rehearing.***

This first question can be divided into two separate and distinct questions: (a) whether section 315(e)(2) bars a successful inter partes review petitioner from making the same arguments in district court that it prevailed on in the inter partes review, and (b) whether the operation of the 35 U.S.C. § 315(e)(2) estoppel is affected by the pendency of an administrative rehearing request. The USPTO addresses those questions in turn.

a. Section 315(e)(2) applies to both successful and unsuccessful petitioners

On its face, the text of § 315(e)(2) is unambiguous and draws no distinction between successful and unsuccessful petitioners:

(e) **Estoppel.–**

(2) **Civil actions and other proceedings**.—*The petitioner* in an inter partes review of a claim in a patent under this chapter *that results in a final written decision under section 318(a)*, or the real party in interest or privy of the petitioner, may not assert either in a civil action arising in whole or in part under section 1338 of title 28 or in a proceeding before the International Trade Commission under section 337 of the Tariff Act of 1930 that the claim is invalid on any ground that *the petitioner* raised or reasonably could have raised during that inter partes review.

35 U.S.C. § 315(e)(2) (emphasis added). By its terms, the § 315(e)(2) bar extends to any petitioner—successful or not—in an inter partes review "that results in a final written decision under § 318(a)." If the petitioner has pursued an inter partes review that resulted in a final written decision, the petitioner may not assert in district court or in the ITC any invalidity ground that was or reasonably could have been raised during the inter partes review, regardless of the *actual* outcome of that decision.

The USPTO acknowledges that the plain language, as explained above, leads to the counterintuitive result that a district court would not be able to consider invalidity arguments the Board found persuasive. But the drafting history of this provision confirms the natural meaning of this text. Prior to the creation of inter partes review in the America Invents Act (AIA) in 2011, Congress provided a similar mechanism for administrative review of issued patents in the form of inter partes reexaminations. Inter partes reexamination decisions, like IPR decisions,

were given preclusive effect in infringement litigation. But the preclusionary provision for inter partes reexaminations, pre-AIA § 315(c), was expressly confined to cases in which patent claims had been finally determined to be "valid and patentable":

> A *third party requester* whose request for an inter partes reexamination results in an order under section 313 [35 U.S.C. § 313] *is estopped* from asserting at a later time, in any civil action arising in whole or in part under section 1338 of title 28, *the invalidity of any claim finally determined to be valid and patentable* on any ground which the third party requester raised or could have raised during the inter partes reexamination proceedings.

35 U.S.C. § 315(c) (pre-AIA) (2011) ("Civil Action") (emphasis added).

In other words, only unsuccessful inter partes reexamination requesters were barred from bringing the previously addressed or addressable challenges in district court. Congress did not carry forward the outcome-determinative "determined to be valid and patentable" language when it wrote § 315(e)(2). Rather, Congress replaced it with language that is indifferent to the outcome: that petitioner is estopped when the inter partes review "results in a final written decision"—win or lose. 35 U.S.C. § 315(e)(2). In short, Congress deleted the precise words that the defendants now seek to add back into the statute, but the best indication of Congress's intent is the change in the statutory text itself. *Stone v. INS*, 514 U.S. 386, 397 (1995) ("When Congress acts to amend a statute, we presume it intends its amendment to have real and substantial effect."); *Bausch & Lomb, Inc. v.*

United States, 148 F.3d 1363, 1367 (Fed. Cir. 1998) ("A change in the language of a statute is generally construed to import a change in meaning….") (citation omitted).

Moreover, the heading of § 315(e), "Estoppel," does not evidence legislative intent to incorporate common law collateral estoppel principles (and thereby an unspoken limitation to unsuccessful petitioners) into § 315(e)(2). That argument places too much weight on what is, in the end, simply a broad subsection heading. Though "statutory titles and section headings 'are tools available for the resolution of a doubt about the meaning of a statute,'" the subchapter heading standing alone "cannot substitute for the operative text of the statute" itself. *Florida Dept. of Revenue v. Piccadilly Cafeterias, Inc.*, 554 U.S. 33, 47 (2008) (citation omitted); *Pennsylvania Dept. of Corrections v. Yeskey*, 524 U.S. 206, 212 (1998) ("[T]he title of a statute . . . cannot limit the plain meaning of the text.") (citation omitted); *Bhd. of R.R. Trainmen v. Baltimore & Ohio R.R. Co.*, 331 U.S. 519, 528 (1947) (the headings of statutory provisions are "not meant to take the place of the detailed provisions of the text").[1]

[1] Indeed, the text of § 315(e)(2) cannot be reconciled with common law collateral estoppel because it estops petitioners on grounds that they raised or "reasonably could have raised"; collateral estoppel applies only to grounds that were "actually litigated and determined." *B&B Hardware, Inc. v. Hargis Indus., Inc.*, ___ U.S. ___, 135 S. Ct. 1293, 1303 (2015), quoting Restatement (Second) of Judgments §27, p. 250 (1980).

The operative statutory text here is "may not assert," which makes no distinction between successful and unsuccessful petitioners. The argument that "may not assert" would not prevent a petitioner from "maintaining" a previously-asserted defense proves too much—if "assert" could be read that way, then unsuccessful petitioners would likewise not be estopped. Moreover, when Congress sought to exclude a class of petitioners from the reach of § 315(e)(2), it did so expressly. *See* 35 U.S.C. § 317(a) (providing exception for petitioners in proceedings that were terminated prior to resulting in a final written decision). In view of the plain language of the operative text, the existence of an exception that does not aid successful petitioners, and the differences between § 315(e)(2) and its inter partes reexamination predecessor (pre-AIA § 315(c)), the provision must be read to apply to successful as well as unsuccessful petitioners. The bare use of the word "estoppel" in the subsection heading cannot create a distinction that is not supported by the statutory text, and ignores the intent reflected in § 317(a) and the change from pre-AIA § 315(c). [2]

The USPTO notes that the Board's Trial Practice Guide does look to collateral estoppel principles, but only for determinations of privity. *See* 77 Fed. Reg. 48759 (Aug. 14, 2012).

[2] In the context of common law assignor estoppel, this Court has likewise made clear that common law notions of estoppel must give way to the plain language of the AIA. *See Arista Networks, Inc. v. Cisco Sys., Inc.*, 908 F.3d 792, 803 (Fed. Cir. 2018) (holding that the "plain language" of § 311(a) "delineates who may file an IPR petition" and that this plain language allows any "person who is

In any event, as the district court noted in *SiOnyx*, the application of § 315(e)(2) to successful petitioners, in many cases, has no "practical effect."[3] *SiOnyx, LLC v. Hamamatsu Photonics K.K.*, 330 F.Supp.3d 574, 600 (D. Mass. 2018). If this Court affirms the Board's unpatentability determination, the challenged claims will be cancelled. 35 U.S.C. § 318(b). Those cancelled claims could no longer be asserted against the successful petitioners or any other party. Accordingly, any co-pending infringement proceeding would be resolved in the petitioner's favor. Conversely, if the court reverses the Board's unpatentability determination, defendants would then become "unsuccessful" petitioners and indisputably subject to estoppel. *SiOnyx*, 330 F. Supp. 3d at 600.[4] Under this

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not the owner of a patent" to file an inter partes review petition, including "an assignor, who is no longer the owner of a patent."); *see also Johnson v. Whitehead*, 647 F.3d 120, 129 (4th Cir. 2011) ("While judicial preclusion rules ordinarily reflect the common law, agency preclusion rules are creatures of statute. Courts must thus refrain from imposing judge-made preclusion principles on agencies unless such a course is dictated by statute.") (citing, *inter alia*, *Astoria Fed. Sav. & Loan Ass'n v. Solimino*, 501 U.S. 104, 108 (1991) and *FCC v. Schreiber*, 381 U.S. 279, 290-91 (1965)).

[3] An administrative law judge at the ITC also applied estoppel to a successful petitioner. *Certain Hybrid Electric Vehicles and Components Thereof*, Inv. No. 337-TA-1042 (USITC Nov. 2, 2017). The case settled (2018 WL 3456237 (USITC Apr. 26, 2018)) after the Commission granted review of that decision. 2017 WL 6350515 (USITC Dec. 8, 2017).

[4] Although some district court cases have stated that § 315(e)(2) estoppel applies to unsuccessful petitioners, they have done so without any examination of whether it also applies to successful petitioners. *See, e.g., Milwaukee Elec. Tool Corp. v. Snap-On, Inc.*, 271 F. Supp. 3d 990, 1027 (E.D. Wis. 2017). As such, they

reasoning, the *SiOnyx* district court estopped defendants from arguing the invalidity of claims on grounds that defendants had prevailed on at the Board, but before all appeals had been exhausted. *Id.*

Contrary to the district court's suggestion in this case, the USPTO's reading of § 315(e)(2) does not require a party "to stand mute" in an infringement proceeding simply because it prevailed before the Board. As explained *infra*, successful petitioners may ask the district court to stay infringement litigation until the Board rehearing and appeals process has been completed and the patent itself has been cancelled. Although a stay of proceedings cannot be guaranteed, successful petitioners have strong arguments that a stay would be appropriate. These arguments include the fact that a final adjudication of the IPR could obviate the need for a trial, as well as (potentially) a post-trial amendment or judgment to account for cancellation of the patent.

b. Section 315(e)(2) estoppel attaches once the PTAB has issued a "final written decision" even if a party seeks rehearing of that decision

The second part of the Court's first amicus question is whether the filing of a rehearing request delays the onset of the § 315(e)(2) bar until a decision is made on the rehearing request. As a preliminary matter, the USPTO's answer to the first

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are not persuasive authority as to whether § 315(e)(2) applies to successful petitioners.

half of the question points to the correct answer for the second half. Thus, if § 315(e)(2) applies only to unsuccessful petitioners, it might make sense to have it apply only after the agency has rendered a truly final decision—that is, disposed of any rehearing request. But because, as the USPTO has argued above, § 315(e)(2) does not distinguish between successful and unsuccessful petitioners, there is no reason to delay estoppel application until the rehearing request has been resolved. Even if the Board decides on a petitioner's rehearing request that it erred and the petitioner's invalidity arguments are in fact meritorious, the petitioner will still be precluded from contesting validity in district court on those grounds, so there is nothing to be gained from waiting to see whether the Board changes its decision.

More fundamentally, as a strictly textual matter, § 315(e)(2) applies to prevent petitioners from litigating in district court any invalidity claim raised in an inter partes review once that proceeding has "result[ed] in a final written decision under section 318(a)." In other words, up until the point at which the Board has rendered a decision on the patentability of any challenged patent claim, which it is required to do at the conclusion of trial, 35 U.S.C. § 318(a), petitioners may continue to assert invalidity defenses in co-pending litigation. But the estoppel

provisions under section 315(e)(2) attach once the IPR proceedings have "result[ed]" in a written decision by the Board.

This is true even though a rehearing request might be filed from a "final written decision." While the filing of a rehearing request renders a "final written decision" non-final and, therefore, unappealable, *see ICC v. Brotherhood of Locomotive Engineers*, 482 U.S. 270, 284-85 (1987); 37 C.F.R. § 90.3(b), the statute nonetheless attaches estoppel as soon as the inter partes review has "result[ed] in" a decision. Thus, the question is not whether a "final written decision" is "final" for purposes of appellate review; the question is only whether, pursuant to § 318(a), a "final written decision" has issued. As with district court litigation, the initial judgment retains its preclusive effect even if additional filings render the decision non-appealable. *See, e.g.*, 18 James Wm. Moore, Moore's Federal Practice § 131.30[2][c][iv], at 131-101 (3d ed. 1998).

Congress could have, but did not, use clear language to provide that the § 315(e)(2) bar applies only after final agency action, including resolution of any rehearing requests. For example, prior to the AIA, estoppel in inter partes reexamination attached only after the challenged claims had been "finally determined to be valid and patentable" after the conclusion of all judicial appeals. *See* 35 U.S.C. § 315(c) (2011); *Bettcher Indus. Inc. v. Bunzl U.S.A. Inc.*, 661 F.3d 629, 642-43 (Fed. Cir. 2011). Congress chose not to carry forward that aspect of

the inter partes reexamination statute, and instead, elected to have estoppel attach as soon as the inter partes review "results in a final written decision." This change illustrates that Congress intended estoppel to attach regardless whether the Board's decision would ultimately be subject to further review. Thus, especially when one considers that Congress made § 315(e)(2)'s bar indifferent to outcome, it can reasonably be inferred that Congress was more concerned with accelerating the effect of the bar than waiting for a final decision, either from the agency or the courts.

Tying estoppel to a decision that is required to ordinarily be reached by a date certain provides predictability and certainty, and is consistent with the AIA's goal of providing a low-cost and speedy alternative to district court litigation. The AIA's authors were particularly concerned about the timing of post-issuance proceedings, and the fact that under the pre-AIA system, "it typically takes three or four years before the PTO decides an inter partes reexamination," and "the decision can then be appealed, which can make the process last from 5 to 8 years." S. Rep. No. 111-18, at 55 (2009) (Minority Views of Sens. Kyl, Feingold, and Coburn). To address these concerns, Congress imposed a 12-month time limit for completion of AIA trials, *see* 35 U.S.C. § 316(a)(11), made estoppel effective against challenges in all other fora upon issuance of the Board's "final written decision under section 318(a)" rather than upon exhaustion of Article III appeals,

see id. § 315(e), and eliminated internal agency appeals of post-issuance review decisions. *See* 157 Cong. Rec. S1376 (Mar. 8, 2011) (Sen. Kyl) (noting that "the AIA's eliminat[ion of] administrative appeals" will "substantially accelerate the resolution of inter partes cases").

By contrast, if estoppel did not attach until the resolution of all requests for rehearing, neither parties nor district courts would be able to readily predict when estoppel might attach. Neither the statute nor the regulations impose a timeframe upon the Board for issuing a rehearing decision. While the Board endeavors to decide a request within two months of filing, extenuating factors can prevent the Board from meeting this goal as illustrated by the 11-month pendency of the rehearing requests in this case. This uncertainty might discourage district courts from staying infringement actions pending decisions at the Board,[5] and would

[5] Trial courts have emphasized that an important factor in deciding whether to stay a civil action is that, upon conclusion of the Board proceeding, "the defendant will be estopped from challenging the validity of the claims on any ground that was, or could reasonably have been, asserted in the inter partes proceeding." *NFC Tech. LLC v. HTC Am., Inc.*, Case No. 2:13-CV-1058-WCB, 2015 WL 1069111, *4 (E.D. Tex. Mar. 11, 2015) (Bryson, J., sitting by designation) (citing § 315(e)(2)). Courts evaluating stays of litigation have thus relied on the fact that the inter partes review machinery allows them to know with reasonable certainty when the USPTO will institute review, *see Oil-Dri Corp. v. Nestle Purina Petcare Co.*, Case No. 15-cv-1067, 2015 WL 13650951, at *1 (N.D. Ill. May 5, 2015), and even to predict a date certain by which the Board will issue a final written decision and the § 315(e)(2) estoppel will take effect. *See Milwaukee Elec. Tool Corp. v. Hilti, Inc.*, 138 F. Supp. 3d. 1032, 1035 (E.D. Wisc. 2015) (granting a stay while noting that "[u]nder the USPTO's statutory schedule, final written decisions on the IPRs are expected by July 31, 2016" at which point the defendants "will be bound

drive up the cost of litigation by keeping otherwise estopped invalidity arguments in play.

The USPTO's view on § 315(e)(2) estoppel here also reflects the reading the Office has given to the sister administrative statutory bar provision at § 315(e)(1). Section 315(e)(1) provides that "[t]he petitioner in an inter partes review . . . that results in a final written decision under section 318(a) . . . may not request or maintain a proceeding before the Office with respect to that claim on any ground that the petitioner raised or reasonably could have raised during that inter partes review." The Board has applied the § 315(e)(1) bar based upon issuance of the final written decision, independent of any pending or possible rehearing request. *See, e.g.*, *Facebook, Inc. v. Uniloc USA, Inc*., IPR2017-01427, Paper 30 (PTAB May 29, 2018) (applying § 315(e)(1) bar based on final written decision in IPR2017-00225 during period for rehearing); *Apple Inc. v. Personalized Media Communications LLC*, 2018 WL 922376, at *2 (PTAB Feb. 15, 2018) (applying § 315(e)(1) bar based upon a separate final written decision for which a rehearing

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by the estoppel provision [at] 35 U.S.C. § 315(e)(2)"); *see also Cypress Semiconductor Corp. v. GSI Tech., Inc*., Case No. 13-cv-02013-JST, 2014 WL 5021100, *1 & 3 (N.D. Cal. Oct. 7, 2014) (relying on date certain for final written decision and related § 315(e) estoppel). Uncoupling the § 315(e)(2) estoppel from the "final written decision" under section 318(a) — an event that reliably occurs 12 months after institution — would eliminate certainty as to when the estoppel will take effect, and would inevitably affect district judges' decisions whether to grant a stay of litigation pending completion of inter partes review.

request had been filed and was "being determined concurrently"); *Valve Corp. v. Ironburg Inventions Ltd.*, 2018 WL 575390, at *1 n.4 & *4 (PTAB Jan. 25, 2018) (applying § 315(e)(1) bar based on separate final written decision with pending rehearing request); *see also Emerson Elec. Co. v. IP Co., LLC*, 2017 WL 2390705, at *1-3 (PTAB May 31, 2017) (precluding institution based on separate final written decision that was on appeal). At least one district court has recognized that "estoppel attaches when the [Board] issues a final written decision under section 318(a)," despite the Board's issuance of a subsequent decision denying rehearing. *See Verinata Health, Inc. v. Ariosa Diagnostics, Inc.*, Case No. 12-cv-05501-SI, 2017 WL 235048, at *5 (N.D. Cal. Jan. 19, 2017); *see also SiOynx*, 330 F. Supp. 3d at 600-01 (rejecting argument that estoppel should not attach in view of pending judicial appeal).

In short, not only does the plain language of the statute provide that estoppel attaches upon decision issuance, but there is also no good reason that Congress would have wanted a petitioner to be able to indefinitely toll the application of the § 315(e)(2) bar by simply filing a rehearing request.

(2) Whether a decision is a "final written decision" under 35 U.S.C. § 315(e)(2) if the period for rehearing under 37 C.F.R. § 42.71(d) has not yet expired.

The final written decisions in the underlying inter partes reviews here all issued on January 17, 2018. *See* Appx2. Appellant Janssen timely filed requests for

rehearing in all three proceedings in February, 2018; the Board denied those rehearing requests on December 3, 2018. *See BTG* Br. at 1. Thus, requests for rehearing were pending when the district court conducted its bench trial between July 23, 2018, and August 2, 2018 (Appx3), and when the court addressed the estoppel issue in its October 31, 2018 decision.

Because the rehearing requests here were filed before the district court trial at which estoppel should have applied, question two is not presented by the facts of this case. However, if reached, the USPTO's answer to question one would largely answer question two. While the USPTO regulations provide 30 days to file a request for rehearing on the final written decision (37 C.F.R. § 42.71(d)(2)) and reset the period for appeal upon refiling of a timely request for rehearing (37 C.F.R. § 90.3(b)(1)), the statute does not condition estoppel attachment on exhausting any rehearing remedy. Thus, § 315(e)(2)'s bar attaches once a final written decision has been issued and the possibility of a rehearing request does not alter or forestall that result.

(3) Whether a PTAB decision on the pending requests for rehearing could moot the estoppel issue.

As explained above, estoppel attaches under § 315(e)(2) as soon as the IPR proceeding results in a written decision as to the patentability of the challenged claims. That remains true even if a party petitions for rehearing. Accordingly, the Board's decision to deny the petitions for rehearing did not affect the application of

§ 315(e)(2) to the district court proceedings. Of course, now that the appeals from the district court actions have been consolidated with the appeals from the inter partes reviews, if this Court upholds the Board's unpatentability findings, and all possible avenues of review of those decisions are exhausted, the estoppel issue need not be addressed.[6]

(4) Whether a district court can stay a case pending the outcome of a request for rehearing of a final written decision and/or appeal from a final written decision.

Yes, district courts can stay a case pending the outcome of a request for rehearing of a final written decision and/or appeal from a final written decision. District courts have broad discretion to manage their dockets, including staying proceedings to accommodate case management considerations. *See, e.g.*, *Clinton v. Jones*, 520 U.S. 681, 706 (1997) ("[A] District Court has broad discretion to stay proceedings as an incident to its power to control its own docket."). And district courts have frequently stayed litigation pending the completion of IPR proceedings or appeals. *See, e.g.*, *Depomed, Inc. v. Purdue Pharma L.P.*, 2016 WL 50505, at *2

[6] The USPTO acknowledges that BTG has argued that even if the patents are finally held invalid, it would still be entitled to damages based on the district court's failure to issue a 35 U.S.C. § 271(e)(4)(a) order to the FDA that would have prolonged BTG's exclusivity. This argument appears to fly in the face of *Fresenius USA., Inc. v. Baxter Int'l, Inc.*, 721 F.3d 1330, 1341-44 (Fed. Cir. 2013), which makes clear that past damages are not available for patents that have been finally held invalid.

(D.N.J. 2016) ("A stay of Depomed's infringement action pending Purdue's IPR appeals would not be an unusual result.").

The Hatch-Waxman Act creates no exception to these principles. Indeed, at least one court has stayed a Hatch-Waxman action until the USPTO issues a final written decision in the IPR proceedings. *Eli Lilly & Co. v. Accord Healthcare Inc.*, 2015 WL 8675158, at *2 (S.D. Ind. Dec. 11, 2015); *see also Abbott Labs. v. Matrix Labs., Inc.*, 2009 WL 3719214, at *3 (N.D. Ill. Nov. 5, 2009) (rejecting arguments that Hatch-Waxman precludes a stay of ANDA litigation). A district court is therefore free to stay an infringement action to await the completion of administrative proceedings on a related inter partes review petition.

CONCLUSION

If this Court addresses BTG's estoppel challenges, the Court should interpret the § 315(e)(2) estoppel to apply to both successful and unsuccessful petitioners, and to attach when the IPR proceeding results in a written decision regardless of any pending or possible request for rehearing.

February 1, 2019

Respectfully submitted,

/s/ Farheena Y. Rasheed

THOMAS W. KRAUSE
Solicitor

FARHEENA RASHEED
Senior Counsel for Patent Law & Litigation

FRANCES M. LYNCH
ROBERT J. MCMANUS
JOSEPH MATAL
Associate Solicitors

U.S. Patent and Trademark Office
Office of the Solicitor
Mail Stop 8, P.O. Box 1450
Alexandria, Virginia 22313
(571) 272-9035

Attorneys for the Director of the United States Patent and Trademark Office

JENNIFER L. UTRECHT
SCOTT R. MCINTOSH
MARK R. FREEMAN
Of Counsel

Attorneys, Appellate Staff
Civil Division, Room 7325
U.S. Department of Justice
950 Pennsylvania Avenue NW
Washington, DC 20530

(202) 514-5048

RULE 32(a)(7)(C) CERTIFICATE OF COMPLIANCE

Pursuant to Federal Rule of Appellate Procedure 32(a)(7), the undersigned certifies that the foregoing **INVITED BRIEF FOR THE DIRECTOR – U.S. PATENT AND TRADEMARK OFFICE AS AMICUS CURIAE IN SUPPORT OF NEITHER PARTY** complies with the type-volume limitation required by the Court's rule. The total number of words in the foregoing brief, excluding the parts exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b), is 4,580 as calculated using the Word® software program.

/s/ Farheena Y. Rasheed
Farheena Y. Rasheed
Senior Counsel for Patent Law & Litigation
U.S. Patent and Trademark Office

CERTIFICATE OF SERVICE

I hereby certify that on February 1, 2019, the foregoing **INVITED BRIEF FOR THE DIRECTOR – U.S. PATENT AND TRADEMARK OFFICE AS AMICUS CURIAE IN SUPPORT OF NEITHER PARTY** was electronically filed using the Court's CM/ECF filing system. Counsel of record was electronically served by and through the Court's CM/ECF filing system pursuant to Fed. Cir. R. 25(e).

/s/ Farheena Y. Rasheed
Farheena Y. Rasheed
Senior Counsel for Patent Law & Litigation
Office of the Solicitor
U.S. Patent and Trademark Office
Mail Stop 8
P.O. Box 1450
Alexandria, Virginia 22313
farheena.rasheed@uspto.gov
571-272-9035

EXHIBIT 3

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.
Petitioner,
v.

SANOFI-AVENTIS DEUTSCHLAND GMBH
Patent Owner.

Patent No. 7,476,652

PETITION FOR *INTER PARTES* REVIEW

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Exhibit No.	Description
1001	U.S. Patent No. 7,476,652, *Acidic Insulin Preparations Having Improved Stability* (filed March 25, 2005) (issued January 13, 2009)
1001A Part I	File History for U.S. Patent No. 7,476,652 Part I
1001A Part II	File History for U.S. Patent No. 7,476,652 Part II
1001A Part III	File History for U.S. Patent No. 7,476,652 Part III
1001A Part IV	File History for U.S. Patent No. 7,476,652 Part IV
1001A Part V	File History for U.S. Patent No. 7,476,652 Part V
1001A Part VI	File History for U.S. Patent No. 7,476,652 Part VI
1002	U.S. Patent No. 7,713,930, *Acidic Insulin Preparations Having Improved Stability* (filed December 4, 2008) (issued May 11, 2010)
1002A	File History for U.S. Patent No. 7,713,930
1003	Expert Declaration of Professor Samuel H. Yalkowsky in Support of Petition for *Inter Partes* Review of Patent No. 7,476,652 and U.S. Patent No. 7,713,930
1003A	*Curriculum Vitae* of Professor Samuel H. Yalkowsky
1003B	Materials Reviewed by Professor Samuel H. Yalkowsky
1004	2001 Physician's Desk Reference ("PDR") Entry for LANTUS®
1004A	Affidavit of Patricia van Skaik for December 1, 2000 date stamp of 2001 PDR received by the Lloyd Library and Museum (Cincinnati, Ohio)
1005	D.R. Owens et al., "Pharmacokinetics of 125I-Labeled Insulin Glargine (HOE 901) in Healthy Men", *Diabetes Care* 23:813-19

Exhibit No.	Description
	(June 2000)
1006	W.D. Lougheed et al., "Physical Stability of Insulin Formulations", *Diabetes* 32:424-32 (May 1983)
1007	2000 FASS Entry for INSUMAN INFUSAT (January 2000)
1007A	Certified English translation for Ex. 1007 (FASS Entry for INSUMAN INFUSAT)
1008	U. Grau and C.D. Saudek, "Stable Insulin Preparation for Implanted Insulin Pumps", *Diabetes* 36:1453-59 (December 1987)
1009	EMEA Public Statement on INSUMAN INFUSAT (February 14, 2000), at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/08/news_detail_001094.jsp&mid=WC0b01ac058004d5c1 (accessed June 1, 2017)
1010	FDA Drug Approval for LANTUS® (NDA 02-1081) (April 20, 2000) at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021081 (accessed June 4, 2017)
1011	P. Gillies et al., "Insulin Glargine", *Drugs* 59:253-60 (February 2000)
1012	U. Derewenda et al. "Phenol Stabilizes More Helix in a New Symmetrical Zinc Insulin Hexamer", *Nature* 338:594-6 (April 1989)
1013	H. Berchtold and R. Hilgenfeld, "Binding of Phenol to R6 Insulin Hexamers", *Biopolymers* 51:165-72 (1999)
1014	J. Brange and L. Langkjær, "Insulin Structure and Stability", in STABILITY AND CHARACTERIZATION OF PROTEIN AND PEPTIDE DRUGS, CASE HISTORIES CHAPTER 11, 315-50 (Vol. 5 of Pharmaceutical Biotechnology) (eds. Y. J. Wang and R. Pearlman) (Plenum Press, New York) (1993)

Exhibit No.	Description
1015	J. Brange et al., "Toward Understanding Insulin Fibrillation", *J. Pharm. Sci.* 86:517-25 (May 1997)
1016	L.S. Jones et al., "Surfactant-Stabilized Protein Formulations: A Review of Protein-Surfactant Interactions and Novel Analytical Methodologies", in THERAPEUTIC PROTEIN AND PEPTIDE FORMULATION AND DELIVERY, ACS SYMPOSIUM SERIES (eds. Z. Shahrokh et al.) (American Chemical Society, Washington D.C.) (1997)
1017	K. Hallas-Moller, "The Lente Insulins", *Diabetes* 5:7-14 (1956)
1018	W.D. Lougheed et al., "Insulin Aggregation in Artificial Delivery Systems", *Diabetologia* 19:1-9 (July 1980)
1019	Excerpts from Handbook of Pharmaceutical Excipients 2nd Edition (eds. A. Wade and P.J. Weller) (American Pharmaceutical Association, Washington) (The Pharmaceutical Press, London) (1994)
1020	W.R. Ashford and S. Landi, "Stabilizing Properties of Tween 80 in Dilute Protein Solutions", *Bull. Parenteral Drug Assoc.* 20:74-81 (1966)
1021	H. Thurow and K. Geisen, "Stabilisation of Dissolved Proteins Against Denaturation at Hydrophobic Interfaces", *Diabetologia* 27:212-18 (1984)
1022	M. Katakam et al., "Effect of Surfactants on the Physical Stability of Recombinant Human Growth Hormone", *J. Pharm. Sci.* 84:713-16 (June 1995)
1023	U.S. Patent No. 4,153,689 "Stable Iinsulin Preparation for Nasal Administration" (Issued May 8, 1979) ("Hirai")
1024	U.S. Patent No. 4,839,341 "Stabilized Insulin Formulations" (Issued June 13, 1989) ("Massey")
1025	E.P. Publication No. 0200383 "An Improved Method for

Exhibit No.	Description
	Administering Insulin" (Issued November 5, 1986) ("Su")
1026	A. Chawla et al. "Aggregation of Insulin, Containing Surfactants, in Contact with Different Materials", *Diabetes* 34:420-24 (May 1985)
1027	Y-C Lee et al., "Effect of Brij-78 on Systemic Delivery of Insulin from an Ocular Device" *J. Pharm. Sci.* 86:430-33 (April 1997)
1028	Y-C Lee et al., "Review on the Systemic Delivery of Insulin via the Ocular Route", *Int'l J. Pharmaceutics* 233:1-18 (February 2002)
1029	M. Heile and D. Schneider, "The Evolution of Insulin Therapy in Diabetes Mellitus", *J. Fam. Pract.* 61 (5 Suppl.: S6-12 (May 2012)
1030	ADIS R&D Profile "Insulin Glargine: Glargine, HOE 71GT15, HOE 71GT80, HOE 901", *Drugs R&D* 2:107-09 (August 1999)
1031	R. Jones, "Insulin Glargine Aventis Pharma", *IDrugs* 3:1081-87 (2000)
1032	I.R. Schmolka, "Poloxamers in the Pharmaceutical Industry", in POLYMERS FOR CONTROLLED DRUG DELIVERY, CHAPTER 10 (CRC Press) (1991)
1033	2001 Rote Liste; Entry for INSUMAN INFUSAT
1033A	Certified Translation of Exh. 1033 (2001 Rote Liste; Entry for INISUMAN INFUSAT)
1033B	Declaration of Hans-Peter Krieger (Deutsche National Bibliothek Librarian) for receipt of 2001 Rote Liste by Deutsche National Bibliothek on February 16, 2001
1034	L. Gatlin and C. Gatlin, "Minimizing Injection Pain & Damage" in INJECTABLE DRUG DEVELOPMENT TECHNIQUES TO REDUCE PAIN AND IRRITATION CHAPTER 17 (eds. P.K. Gupta and G.A. Brazeau) (CRC Press) (1999)

Exhibit No.	Description
1035	2004 CNN Money article regarding Aventis Pharma merger with Sanofi-Synthelabo to create Sanofi-Aventis, the parent corporation of '930 patent assignee Sanofi-Aventis Deutschland GmbH at http://money.cnn.com/2004/04/26/news/international/aventis_sanofi/ (accessed June 2, 2017)

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Mylan") petitions for *Inter Partes* Review ("IPR") of claims 1-25 of U.S. Patent No. 7,476,652 to Brunner-Schwarz et al., titled "Acidic Insulin Preparations Having Improved Stability" ("the '652 patent," Ex. 1001). 37 U.S.C. §311.

By a preponderance of the evidence, this Petition proves the prior art renders unpatentable claims 1-25 of the '652 patent. An ordinarily skilled artisan ("PHOSITA"[1]) would have reason to combine the LANTUS® (Insulin Glargine) label [Ex. 1004], which was approved in 2000 and included each component claimed except for a polysorbate or poloxamer, with Lougheed [Ex. 1006], the 2000 FASS Insuman Infusat entry [Ex. 1007 and 1007A] or Grau [Ex. 1008], which provided a reasonable expectation of success that adding a non-ionic surfactant to an insulin formulation would inhibit or eliminate the well-known and recognized tendency for insulin to aggregate. The challenged claims were also obvious to a PHOSITA in view of Owens [Ex. 1005] and Lougheed, the FASS Insuman Infusat entry or Grau.

II. MANDATORY NOTICES

A. Real Parties-In-Interest (37 C.F.R. §42.8(b)(1))

[1] All references herein to the knowledge or understanding of a PHOSITA or a PHOSITA's interpretation or understanding of a prior art reference are as of the earliest possible priority date unless specifically stated otherwise.

Mylan's real parties-in-interest are Mylan Pharmaceuticals Inc., Mylan Inc., Mylan GmbH, Mylan N.V., Biocon Research Ltd. and Biocon Ltd.

Mylan Pharmaceuticals Inc., Mylan Inc., and Mylan GmbH are subsidiaries of Mylan N.V.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Mylan is not a party to any litigation related to the '652 patent. The '652 patent is related to U.S. Patent No. 7,713,930 and U.S. Patent Application No. 12/773,356 (now abandoned).

C. Identification of Counsel (37 C.F.R. §42.8(b)(3)) and Service Information (37 C.F.R. §42.8(b)(4))

Lead Counsel	Back-Up Counsel
Jeffrey W. Guise, Reg. No. 34,613 WILSON SONSINI GOODRICH & ROSATI 650 Page Mill Road, Palo Alto, CA 94304 Tel.: 858-350-2300 Fax: 858-350-2399 Email: jguise@wsgr.com	Douglas Carsten, Reg. No. 43,534 WILSON SONSINI GOODRICH & ROSATI 650 Page Mill Road, Palo Alto, CA 94304 Tel.: 858-350-2300 Fax: 858-350-2399 Email: dcarsten@wsgr.com Richard Torczon, Reg. No. 34,448 WILSON SONSINI GOODRICH & ROSATI 650 Page Mill Road, Palo Alto, CA 94304 Tel.: 202-973-8800 Fax: 202-973-8899 Email: rtorczon@wsgr.com Lorelei Westin, Reg. No. 52,353 WILSON SONSINI GOODRICH &

	ROSATI 650 Page Mill Road, Palo Alto, CA 94304 Tel.: 858-350-2300 Fax: 858-350-2399 Email: lwestin@wsgr.com Clark Lin, Reg. No. 67,024 WILSON SONSINI GOODRICH & ROSATI 650 Page Mill Road, Palo Alto, CA 94304 Tel.: 858-350-2300 Fax: 858-350-2399 Email: clin@wsgr.com Nancy Zhang, Reg. No. 69,463 WILSON SONSINI GOODRICH & ROSATI 650 Page Mill Road, Palo Alto, CA 94304 Tel.: 650-493-9300 Fax: 650-493-6811 Email: nzhang@wsgr.com

Please direct all correspondence to lead counsel and back-up counsel at the contact information above. Mylan consents to electronic mail service at jguise@wsgr.com and dcarsten@wsgr.com. A power of attorney pursuant to 37 C.F.R. §42.10(b) accompanies this petition.

III. CERTIFICATIONS (37 C.F.R. §42.104(a))

Mylan certifies that the '652 patent is available for IPR and that Mylan is not barred or estopped from requesting IPR on the identified grounds.

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED

Mylan requests *inter partes* review and cancellation of claims 1-25 of the '652 patent under pre-AIA § 103, as Mylan's detailed statement of the reasons for the relief requested sets forth, supported with exhibit copies, and the Declaration of Dr. Samuel Yalkowsky [Ex. 1003].

The challenged claims relate to an insulin glargine formulation, specifically a formulation created through the simple addition of a polysorbate or poloxamer to a then-commercially available insulin glargine formulation. Claims 1-25 of the '652 patent are unpatentable on these grounds:

Ground	Claims and Basis
1	Claims 1-25 as obvious over the LANTUS® label [Ex. 1004] and Lougheed [Ex. 1006]
2	Claims 7 and 24 as obvious over the LANTUS® label and the 2000 FASS Insuman Infusat entry [Ex. 1007 and 1007A]
3	Claims 7 and 24 as obvious over the LANTUS® label and Grau [Ex. 1008]
4	Claims 1-25 as obvious over Owens [Ex. 1005] and Lougheed
5	Claims 7 and 24 as obvious over Owens and the 2000 FASS Insuman Infusat entry
6	Claims 7 and 24 as obvious over Owens and Grau

V. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. Summary of the Argument

Researchers have been working since the discovery of insulin in the 1920s to provide diabetic patients with therapeutic insulin preparations that allow constant and consistent glycemic control. Ex. 1003 ¶¶92-97. The development of variant insulin

compositions, including long-acting, controlled release basal insulin analogs, and fast-acting insulin was critical for achieving long-term control of blood sugar levels. *Id.*

Basal insulin glargine (LYS2963016 or HOE 901), developed and patented in the early 1990s, is an example of a biosynthetic recombinant human insulin analogue (Gly(A21)-Arg(B31)-Arg(B32)). *Id.* ¶¶124-28. Insulin glargine differs from human insulin at position 21 (glycine substitution for asparagine) and addition of two arginines at the C-terminal, which results in an altered acidic isoelectric point, as well as a predominantly monomeric insulin form in solution. *Id.* Because of its lowered solubility at neutral pH, insulin glargine precipitates upon injection into a subcutaneous tissue (a relatively neutral environment), resulting in controlled release and a longer time of action. *Id.*; Ex. 1004, 3. Insulin glargine was approved as a therapeutic by the U.S. Food and Drug Administration (FDA) in April 2000. *See* FDA Drug Approval for NDA 021081 [Ex. 1010].

Insulin glargine's mechanism of action centers on its altered isoelectric point, resulting in the therapeutic preparation being more soluble in an acidic environment; by contrast, native human insulin formulations are more soluble at neutral pH. *See* Gillies [Ex. 1011], 2; Ex. 1003 ¶125. Thus, insulin glargine is provided and stored as an acidic (pH 4.0) solution with a predominantly monomeric form. *See* Ex. 1004, 3; Ex. 1003 ¶125. Upon administrating the acidic insulin glargine solution, the neutral environment of the patient's subcutaneous tissue causes insulin glargine to precipitate

at the site of injection, effectively prolonging its absorption into the bloodstream. *Id.* Adding zinc prolonged the release of active insulin monomers. Preservatives (*e.g.*, m-cresol) and isotonic agents (*e.g.*, glycerol) were extensively used to further stabilize insulin formulations. *See* Owens [Ex. 1005], 3; Derewenda [Ex. 1012], 1; Berchtold [Ex. 1013], 1; Brange and Langkjær [Ex. 1014], 20; Ex. 1003 ¶125. Patients administered insulin glargine display a 24-hour duration of action with a relatively flat profile over the measured time period. Ex. 1004, 3.

While insulin precipitation *in vivo* can be useful for prolonged therapeutic effect, insulin aggregation before injection (such as during storage) can adversely affect its biological activity, including the well-known and inherent tendency of insulin products to aggregate during storage or agitation of the pharmaceutical solution. *See, e.g.*, Lougheed [Ex. 1006], 1 ("Unfortunately, the tendency of insulin to aggregate during storage in and delivery from [infusion] devices remains one of the fundamental obstacles to their prolonged clinical use."); Brange and Langkjoer [Ex. 1014], 8 ("The inherent tendency of insulin to undergo conformational changes resulting in aggregation and formation of a viscous gel or insoluble precipitates was observed early on in the insulin era."); Ex. 1003 ¶¶103-08. Factors known to contribute to insulin aggregation (or fibrillation) include acidic pH environments, as well as the prevalence of insulin in a monomeric form, primarily due to exposed hydrophobic surface areas. *See, e.g.*, Brange [Ex. 1015], 3 ("[M]onomers [were] the

least stable species and therefore more likely than dimers and hexamers to undergo conformational changes at hydrophobic interfaces.").

Insulin aggregation, which differs from the formation of relatively stable insulin dimers and hexamers in solution, contributes to the formation of high-molecular weight polymers including desamido insulin, which can lead to decreases in biological activity of the insulin preparation. Ex. 1006, 1. In fact, labels for insulin preparations, such as insulin glargine, have long warned patients not to use the product unless "the solution is clear and colorless with no particles visible", *i.e.*, no aggregation of insulin has occurred. Ex. 1004, 5-6. Moreover, insulin glargine would have also been expected to aggregate because of the prevalence of monomeric forms of insulin glargine and its acidic pH environment. *See* Ex. 1003 ¶¶105-08, 126.

Thus, it was long and well-known that insulin had a tendency to aggregate. That inherent characteristic, recognized for decades, hampered efforts to develop insulin solutions, for example, for therapeutic mechanical and automatic infusions. Skilled artisans have expended significant effort in researching and testing ways to prevent insulin aggregation during storage and use. Ex. 1003 ¶¶109-23. In the early 1980s, Lougheed and colleagues performed experiments designed to test insulin formulations under the most severe storage conditions, including varying storage materials (such as copper, titanium and rubber), bacteriostatic agents (cresol, phenol and glycerol), and using different non-ionic, anionic and ionic surfactants to combat

insulin aggregation. Lougheed concluded that aggregate formation was inhibited by the tested nonionic detergents, including Brij 35, Lubrol WX, Triton X100, Tween 20 and Tween 80, and the anionic detergent sodium dodecyl sulfate (SDS). Lougheed [Ex. 1006], 7. Other prior art references confirmed the early findings of Lougheed concluding that adding surfactants to insulin formulations would reduce aggregation and have no adverse effect on the biological activity of insulin. Ex. 1003 ¶¶109-23. In fact, Brange et al. concluded that "[s]tabilization of the insulin hexameric structure and blockage of hydrophobic interfaces by addition of surfactants are the most effective means of counteracting insulin fibrillation." Brange [Ex. 1015], Abstract; Ex. 1003 ¶109. Accordingly, adding a surfactant to known insulin formulations would have been well-known and routine to PHOSITAs. Ex. 1003 ¶¶109-23.

The fact that non-ionic surfactants stabilize and inhibit aggregation in protein solutions is not surprising. Non-ionic surfactants, including polysorbates and poloxamers, have long been used to stabilize commercially available and FDA-approved human protein and polypeptide pharmaceutical formulations because of their stabilizing effects, low toxicity, and pH independence. *See* Ex. 1003 ¶¶111-15. ("Based on their use in reducing aggregation in other protein formulations as well as their safety, one of ordinary skill in the art would consider polysorbates and poloxamers in formulating insulin."). Jones noted that the Physician's Desk Reference ("PDR") in 1994, well before the earliest priority date of September 9,

2002, included commercial formulations incorporating non-ionic surfactants such as the claimed polysorbate 20 and polysorbate 80:

Table I. Nonionic Surfactants Used in the Pharmaceutical Industry

Chemical Name	Commercial Name	Final Formulation Usage	Quantity	Manufacturer
Polysorbate 20	Tween 20	Actimmune (Interferon gamma-1b)	0.1 mg/ml	Genentech
Polysorbate 40	Tween 40			
Polysorbate 60	Tween 60			
Polysorbate 80	Tween 80	Tubersol (Tuberculin purified protein derivative diagnostic antigen)	0.0005%	Connaught Laboratories
Polysorbate 80	Tween 80	RhoGAM (Rh_0 (D) Immune Globulin)	0.01%	Ortho Diagnostics Systems
Polysorbate 80	Tween 80	Neupogen (Filgrastim)	0.004%	Amgen
Polysorbate 80	Tween 80	Activase (Recombinant Alteplase)	0.11 mg/ml	Genentech
Polysorbate 80	Tween 80	Koate-HP (Factor VIII)	< 25 ppm	Miles Biologicals
Polysorbate 80	Tween 80	Kogenate (Recombinant Antihemopphilic Factor)	<600 µg / 1000 IU	Miles Biologicals
Cetomacrogol 1000	Brij			
Polyethylene Glycol	PEG			

(Adapted from Bam) (15). Final Formulation Usage and Quantity data compiled from *Physicians Desk Reference (PDR)*, 48th Edition, 1994 and is by no means complete. Information regarding specifics of these and other approved excipients for pharmaceutics found in several handbooks (16-19).

See Ex. 1016, 3.

Moreover, Insuman Infusat, an insulin product approved by the EMA (European Medicines Agency) in 1997 and "specially designed for use in external portable insulin pumps", was a commercially available insulin therapeutic in at least Austria, France, Sweden, Finland and Germany. *See* EMEA Public Statement [Ex. 1009], 1. Insuman Infusat included a non-ionic surfactant well before the earliest priority date of the '652 patent. *See, e.g.*, 2000 FASS Insuman Infusat Entry [Ex. 1007 and 1007A], 5 (inclusion of poly(oxyethylene, oxypropylene)glycol to biosynthetic human insulin formulation); Insuman Infusat 2001 Rote Liste Entry [Ex.

1033, 1033A], 6 (inclusion of poloxamer 171 in human recombinant insulin solution). Insuman Infusat was developed by Hoescht AG, and marketed by Sanofi-Aventis.

It is beyond reasonable dispute that non-ionic surfactants were used in commercially-available insulin formulations for inhibiting protein aggregation long before the priority date of the '652 patent's claims. Thus a PHOSITA would have had reason to improve commercially-available insulin glargine formulations (*see*, *e.g,* LANTUS® 2000 label [Ex. 1004] and Owens [Ex. 1005]) by anti-aggregation additives, such as Brij 35, Lubrol WX, Triton X100, Tween 20, Tween 80, poloxamer 171, poloxamer 181 and other known surfactants, which were used routinely to inhibit aggregation and formation of particles in peptide and protein-containing formulations. Ex. 1003 ¶128. The challenged '652 patent claims were obvious.

B. '652 Patent--Background

1. The '652 Patent

The '652 patent issued January 13, 2009 as a continuation of an earlier-abandoned U.S. patent application (U.S. Patent Appl. No. 10/461,740) (filed June 13, 2003), which claimed priority to U.S. Provisional Appl. No. 60/409,336, filed September 9, 2002, and DE10227232, filed June 18, 2002, the '652 patent's earliest possible priority date.

The '652 patent issued with 25 claims. Claims 1, 7 and 24 are independent claims, all claiming a pharmaceutical formulation comprising:

- Gly(A21), Arg(B31), Arg (B32)-human insulin (*i.e.*, insulin glargine)
- At least one chemical entity chosen from a polysorbate or poloxamer
- At least one preservative
- Water
- pH of the insulin glargine formulation in the range from 1 to 6.8 (claims 1 and 7) or 3.5 to 4.5 (claim 24).

Claim 1 limits the formulation to a polysorbate chosen from polysorbate 20 or polysorbate 80. Claim 24 limits the formulation to the preservative cresol.

Although independent claims 7 and 24 are interspersed within the claim set, all of the dependent claims ultimately depend from independent claim 1 only. The dependent claims recite various chemical entities of the insulin glargine formulation of claim 1, such as polysorbate 20 (claim 2) "in an effective amount to reduce turbidity" (claim 8). Many of the additional chemical entities recited in the dependent claims include compounds that are commonly found in insulin formulations, including a preservative such as phenol (claim 3), cresol (claim 4), or a Markush group of preservatives including "phenol, cresol, chlorocresol, benzyl alcohol, and parabens" (claim 11). Claims 5 and 6 further include other common additives of commercially available insulin formulations, including zinc (claim 5), a buffer (claim 13), including "TRIS, phosphate, citrate, acetate and glycylclycin" (claim 14), "in a concentration of 5-250 mM" (claim 22), sodium chloride (NaCl) in a concentration of

up to 150 mM (claim 21) or "at least one isotonicizing agent") (claim 6). Claim 12, which depends from claim 6, lists "mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride, and glycerol" as isotonicizing agents, common additives in parenteral formulations. Claim 25 further includes "one or more excipients chosen from acids, alkalis and salts" to the claimed formulation of independent claim 1.

Claims 9 and 10 further limit the acidic pH range of independent claim 1 to "3.5 to 6.8" (claim 9) and "3.5 to 4.5" (claim 10). Claims 15 to 18 limit concentrations or amounts of certain agents or excipients in the claimed pharmaceutical formulation, including insulin glargine "in a concentration of 60-6000 nmol/ml" (claim 15) and insulin glargine "in a concentration of 240-3000 nmol/ml" (claim 16). The polysorbate 20 and polysorbate 80 concentrations of claim 1 are limited to 5-200 μg/ml (claim 17), 5-120 μg/ml (claim 18) and 20-75 μg/ml (claim 19).

Claims 20 and 23 recite the excipients and concentrations of claims 12 and 6, respectively. Claim 20 recites "[t]he pharmaceutical formulation as claimed in claim 12, wherein at least one isotonicizing agent is chosen from glycerol and mannitol and wherein said at least one isotonicizing agent is present in a concentration of 100-250 mM." Claim 23 recites "[t]he pharmaceutical formulation as claimed in claim 6, wherein the at least one chemical entity comprises polysorbate 20, at least one preservative is cresol, and the pharmaceutical formulation has a pH in the acidic range

from 3.5 to 4.5.

The well-known issue of insulin aggregation was fully acknowledged by the '652 patent, where "[e]specially at acidic pH, insulins . . . show a decreased stability and an increased proneness to aggregation on thermal and physicomechanical stress, which can make itself felt in the form of turbidity and precipitation (particle formation)." Ex. 1001, 3:2-7, citing to Brange [Ex. 1015]. The '652 patent further describes known sources of insulin aggregation, including hydrophobic surfaces that insulin molecules commonly encounter, such as glass vial walls, rubber or silicone stoppers, and contact with air. Ex. 1001, 3:8-14.

Moreover, while the '652 patent acknowledges such issues, the patent specification fails to acknowledge, and the applicants failed to inform the Patent Office, of the nearly identical prior art insulin glargine formulation that was known and available to the public more than one year before the earliest priority date of the '652 patent, the assignee's prior use of poloxamer in an insulin formulation or the numerous prior art references acknowledging aggregation issues and providing nonionic surfactants as a proven solution to such issues. The only difference between the prior art insulin glargine formulation and the '652 patent claims is the addition of a surfactant, a well-known and proven solution to the well-known and common problem of insulin aggregation.

2. Brief Overview of the '652 Patent's Prosecution History

The '652 patent issued from Application No. 11/089,777 ("the '777 application"). During prosecution, the PTO rejected the '777 application's claims for anticipation, obviousness and lack of written description. The rejection did not include the Lantus® 2000 label [Ex. 1004], Owens [Ex. 1005], Lougheed [Ex. 1006], the FASS Insuman Infusat entry [Ex. 1007] or Grau [Ex. 1008], asserted here. Lougheed was disclosed in an information disclosure statement, but not applied. *See* Ex. 1001A, 67.

C. Level of Ordinary Skill in the Art

The invention's field involves inhibition of insulin aggregation and increased stability in insulin formulations. A PHOSITA would have held an M.S. or Ph.D. or equivalent in pharmacology, pharmaceutical sciences, or a closely related field; or an M.D. with practical academic or industrial experience in peptide injection formulations or stabilizing agents for such formulations. *See, e.g.*, Ex. 1003 ¶¶31-34. A PHOSITA would have, for example, the educational background above with experience in surfactants commonly used in peptide injection formulation, as well as an understanding of factors that contribute to the molecule's instability. *Id*. This experience is consistent with the types of problems encountered in the art, which would have included peptide aggregation and instability, impact of stabilizing agents and additives on peptide aggregation, and compatibility with injection or storage equipment materials, for example. *Id*. A PHOSITA may have also consulted

with one or more team members of experienced professionals to develop an insulin formulation resistant to the well-known aggregation propensities of insulin molecules. *Id*. A PHOSITA would have been well-versed in the field's literature that was available as of the priority date. *Id*.

D. Claim Construction

The '652 patent claims presumably possess their "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. §42.100(b). Under the broadest reasonable construction, a PHOSITA would understand the claim terms below at least include the following meanings.[2]

"A Pharmaceutical Formulation". All claims require a "pharmaceutical formulation" Mylan notes that the claims are not limited to a specific use or method related to the claimed pharmaceutical formulation. Accordingly, any pharmaceutical formulation that recites the limitations of the challenged claims, regardless of the

[2] Without taking a position here on whether the claims are sufficiently definite, Mylan notes that even when the metes and bounds of a claim are indefinite, the Board nevertheless determines whether embodiments plainly within the scope of the claim would have been obvious. *Ex parte Tanksley*, 26 USPQ2d 1384, 1387 (BPAI 1991) (embodiment within scope despite indefiniteness); *Ex parte Sussman*, 8 USPQ2d 1443, 1444 n.* (BPAI 1988) (affirming obviousness despite indefinite claim format).

application or use of the pharmaceutical formulation, would be relevant to the patentability of the challenged claims.

"Polysorbate" or "Poloxamer". The independent claims each contain reference to a "polysorbate" or a "poloxamer." A PHOSITA would understand "polysorbate" or "poloxamer" to refer to classes of compounds, which are used as, for example, surfactants, including nonionic surfactants. *See* Ex. 1003 ¶¶53-57. The '652 patent lists compounds that are "pharmaceutically customary surfactants" as preferred, including:

> [P]artial and fatty acid esters and ethers of polyhydric alcohols such as of glycerol, sorbitol and the like (Span®, Tween®, in particular Tween® 20 and Tween® 80, Myrj®, Brij®), Cremophor® or poloxamers.

Ex. 1001, 3:52-56. Because claims 7 and 24 require only "at least one chemical entity chosen from polysorbate and poloxamers", under the broadest reasonable interpretation of the claim, this limitation would be met by *any* polysorbate or poloxamer.

"Polysorbate 20" or "Polysorbate 80". Independent claim 1 recites to two polysorbate compounds: polysorbate 20 and polysorbate 80. Polysorbate 20 is a nonionic surfactant formed by the ethoxylation of sorbitan before the addition of lauric acid, and has been commonly used in a number of pharmacological applications, including parenteral formulations. *See* Ex. 1003 ¶¶53-54. Polysorbate 80 is also a nonionic surfactant used in parenteral formulations, and is synthesized

from polyethyoxylated sorbitan and oleic acid. *Id*. Furthermore, a PHOSITA would understand that the commercial names for polysorbate 20 and polysorbate 80 include Tween® 20 and Tween® 80, respectively, among other commercial and chemical names. *Id.*

E. Patents and Printed Publications Relied On In This Petition

Mylan relies on the following patents and printed publications:

1. LANTUS® (Insulin Glargine) 2000 Product Label ("LANTUS® 2000 Label") [Ex. 1004 and 1004A]

LANTUS® (insulin glargine) was approved on April 20, 2000. The product label submitted with the approval published in a learned periodical more than one year before the earliest priority date of the '652 patent. *See* Ex. 1004A, Affidavit of Patricia van Skaik establishing at least December 1, 2000 publication date; Ex. 1003 ¶¶129-33.

The LANTUS® 2000 Label discloses insulin glargine as a recombinant DNA insulin that "differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain," *i.e.*, Gly(A21)-Arg(B31)-Arg(B32)-human insulin. Ex. 1004, 3. The LANTUS® 2000 Label states "[e]ach milliliter of LANTUS (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water" with a pH of approximately 4. *Id*. The

LANTUS® 2000 Label contains two warnings that "LANTUS must only be used if the solution is clear and colorless with no particles visible." *Id.*, 5-6.

2. Owens, D.R., et al., "Pharmacokinetics Of ^{125}I-Labeled Insulin Glargine (HOE 901) In Healthy Men: Comparison With NPH Insulin And The Influence Of Different Subcutaneous Injection Sites," Diabetes Care. 2000 Jun;23:813-19 ("Owens") [Ex. 1005]

Owens published in a learned periodical more than one year before the earliest priority date of the '652 patent. Owens described clinical studies designed to determine the subcutaneous absorption rates of insulin glargine (referred to as HOE 901) with 15, 30, and 80 microgram/mL of zinc. Ex. 1005, Abstract; Ex. 1003 ¶¶134-37.

Owens described insulin glargine, or HOE 901, as "a di-arginine (30^{B}a-L-Arg-30^{B}b-L-Arg) human insulin analog in which asparagine at position 21^{A} is replaced by glycine. This achieves an increase in the isoelectric point from pH 5.4 (native insulin) to 7.0 and stabilization of the molecule. When injected as a clear acidic solution (pH 4.0), insulin glargine undergoes microprecipitation in the subcutaneous tissue, which retards absorption." Ex. 1005, 1.

For one of the clinical studies, Owens disclosed the following preparation of insulin glargine:

> The recombinant human insulin analog formulations insulin glargine[15] and **insulin glargine**[80] (Hoechst AG) were also administered from 5-ml vials, with each 1-ml suspension containing **21A-Gly-30^{B}a-L-Arg-30^{B}b-L-**

> **Arg**-human insulin equimolar to **100 U human insulin**, together with **m-cresol** and **glycerol at pH 4.0**, with **15 and 80 µg/ml (2.295 and 12.24 µmol/l) zinc**, respectively.

Id., 3 (emphasis added). Thus, Owens disclosed an insulin glargine formulation containing 100 U/mL insulin glargine, m-cresol, and glycerol with 2.295, 4.59 and 12.24 µmol/L zinc at pH 4.0 well before the earliest priority date of the '652 patent. *Id*., 3-4.

3. Lougheed, W.D., at al. "Physical Stability of Insulin Formulations," Diabetes. 1983 May;32(5):424-32. [Ex. 1006]

Lougheed published in May 1983, more than one year before the earliest priority date of the '652 patent, in a learned periodical. Ex. 1003 ¶¶138-46. Lougheed recognized that "the tendency of insulin to aggregate during storage in and delivery from [infusion] devices remains one of the fundamental obstacles to [the] prolonged clinical use [of insulin]". Ex. 1006, 1. Lougheed recognized that aggregates forming during storage could decrease biological activity "primarily [due] to the formation of high-molecular weight polymers of insulin and desamido insulin." *Id.* Lougheed thus investigated "the effects of physiologic and nonphysiologic compounds on the aggregation behavior of crystalline zinc insulin (CZI) solutions." *Id.*

Lougheed found that Tween, a polysorbate, as well as the broader class of "nonionic and ionic surfactants containing the hydrophobic group, $CH_3(CH_2)_N$,

with N = 7-16," stabilized crystalline zinc insulin (or CZI) formulations, and further concluded that "anionic and nonionic surfactants containing appropriately long hydrophobic groups demonstrated the greatest degree of stabilization." *Id*. Lougheed tested "[n]onionic, cationic, and ionic detergents (both physiologic and synthetic) as stabilizers in view of their known protein-solvation characteristics and their potential to constrain the conformation of insulin and other proteins in aqueous solution." *Id*., 2.

As depicted in Table 3, Lougheed compared the stabilities of formulations containing various nonionic detergents, including Tween 20 and Tween 80, which are also known as polysorbate 20 and polysorbate 80. Lougheed noted that insulin "aggregate formation was inhibited by the nonionics; Brij 35 (0.1% vol/vol), Lubrol WX (0.1% vol/vol), Triton X 100 (0.02% vol/vol), **Tween 20 (0.01% vol/vol), Tween 80 (1% vol/vol)**, and the anionic; SDS (0.05% wt/vol in 0.9% NaCI) and SDS (1% wt/vol)." *Id*., 3-4 (emphasis added). Accordingly, Lougheed disclosed at least the use of Tween 20 (*i.e.*, polysorbate 20) and Tween 80 (*i.e.*, polysorbate 80) to reduce insulin aggregation and particle formulation. *Id.*, 7.

4. FASS 2000 Entry for Insuman Infusat, (January 2000) ("Insuman Infusat") [Ex. 1007 and 1007A]

Insuman Infusat, a commercially available human insulin product distributed by Aventis Pharma[3] in 2001, was published in the Swedish FASS ("Farmaceutiska Specialiteter I Sverige" (Swedish Drug Formulary)) by January 2000, *i.e.*, more than one year before the earliest priority date of the '652 patent. Ex. 1003 ¶¶147-49.

Insuman Infusat, available in 3.15 milliliter ampules containing 100 international units (I.E.) per milliliter recombinant human insulin, was supplied as an injectable solution for the treatment of diabetes mellitus. Insuman Infusat components included: "Insulin for human use (biosynthetic) 100 units (3.5 mg) zinc chloride 0.058 mg, trometamol 6 mg, glycerol 20 mg, poly(oxyethylene, oxypropylene)glycol 0.01 mg, preservative (phenol 2.7 mg), hydrochloric acid 3.7 mg, water for injection up to 1 ml." Ex. 1007A, 5.

The FASS Insuman Infusat entry states that the formulation was specially made to inhibit aggregation in insulin pumps: "**Properties of the pharmaceutical**

[3] Aventis Pharma merged with Sanofi-Synthelabo in 2004 (*see, e.g.*, http://money.cnn.com/2004/04/26/news/international/aventis_sanofi/ (accessed June 2, 2017)) [Ex. 1035] to create Sanofi-Aventis, the parent corporation of '930 patent assignee Sanofi-Aventis Deutschland GmbH.

form. Addition of a stabilizer poly(oxyethylene, oxypropylene), glycol, prevents precipitation and flocculation of the insulin. This makes INSUMAN INFUSAT particularly suited for use in insulin pumps since the risk of clogging in the catheter with resulting loss of the intended effect is minimized." *Id*., 7.

5. Grau, U. and Saudek, C.D., "Stable Insulin Preparation for Implanted Insulin Pumps" Diabetes. 1987 December; 36:1453-59 ("Grau") (Ex. 1008)

Grau published more than one year before the earliest priority date of the '652 patent in a learned periodical. Ex. 1003 ¶¶150-57. Like Lougheed, Grau recognized the issues with stability of insulin formulations:

> The stability of insulin has been a significant impediment in the development of mechanical medication-delivery devices for diabetes. *An inherently fragile protein, insulin has a tendency to precipitate, aggregate in high-molecular weight forms, and denature*.

Ex. 1008, 1 (emphasis added). Grau investigated the ability of the poloxamer Genapol (polyethylene-polypropylene glycol) to inhibit aggregation of insulin in pump catheters.

Grau used a "pH-neutral buffered insulin formulation containing either 100 or 400 IU/ml semi-synthetic human insulin, 27.8 or 111 μg/ml zinc ions (for U-100 and U-400 insulin, respectively) with 2 mg/ml phenol as a preservative, 16 mg/ml glycerol as an isotonicity agent, 50 mM of tris-(hydroxymethyl)-aminomethane (Tris) buffer, and 10 μg/ml polyethylene-polypropylene glycol (Genapol, Hoechst

AG, Frankfurt, FRG)." *Id.*, 1. The insulin formulations were tested on a shaking platform in a programmable implantable medication system (PIMS), which pumped the test formulations into a glass vial at a constant rate throughout the 10+ months of testing. *Id.*, 2-3. Insulin aggregation in PIMS systems was also tested *in vivo* in dogs implanted with the insulin delivery devices. *Id.* The insulin formulation was analyzed for precipitates using scanning electron microscopy and X-ray microanalysis, as well as for biological activity/potency in rabbits. *Id.*, 3-4.

Grau found that insulin concentration, chemical stability and biological potency were maintained when tested both *in vitro* and *in vivo* in PIMS-implanted dogs. *See, e.g.*, Grau [Ex. 1008], 4-5, Tables 2-3. Grau reported that changes to the poloxamer-containing insulin formulations "were comparable to those seen in insulin stored in a glass vial at 37 ^{o}C without movement." *Id.*, 4. Grau found that the "[s]urfaces were clean of apparent precipitate even in remote corners." *Id.*, 5. Grau moreover noted that the "[g]lycemic control of [the] diabetic dogs was good … [with] no trend toward either worse diabetic control or increased insulin dosage between refills …". *Id.* Grau concluded that "Genapol, a surface-active polyethylene-propylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces…. The data demonstrate good stability in accelerated laboratory tests and after as long as 5 mo between refills in vivo." *Id.*, 6.

F. The Prior Art Renders The Challenged Claims Obvious

Before the earliest priority date of the '652 patent, Sanofi-Aventis (the patent assignee) published the details of its commercialized LANTUS® product, an insulin glargine formulation nearly identical to the claimed formulation: the only ingredient missing from the commercially available formulation was the claimed polysorbate or poloxamer (*e.g.*, polysorbate 20 or polysorbate 80 of claim 1). Ex. 1003 ¶162. However, the well-known propensity for insulin aggregation especially at acidic pH was a recognized "fundamental obstacle" in the development of commercial insulin, and was studied well before the earliest priority date of the '652 patent. *Id.* ¶¶103-08. These numerous studies disclosed the use of polysorbates and poloxamers to inhibit insulin aggregation. *Id.* ¶¶109-23. In addition, poloxamer was actually used in a commercially available human insulin formulation sold under the brand name INSUMAN INFUSAT, by Aventis Pharma, for the prevention of insulin aggregation, as disclosed in its Swedish FASS and German Rote Liste label, well before the priority date of the '652 patent. *Id.* ¶122.

In other words, more than a year before the '652 patent's earliest filing date, the details of a commercially available insulin glargine formulation and solutions for inhibiting insulin aggregation of insulin in solution were known, published, and approved for administration as a therapeutic agent for treatment of diabetes. Furthermore, the copious body of work instructing precisely how to solve insulin

aggregation demonstrates that inhibition of insulin aggregation with polysorbates and poloxamers added to a commercially available insulin product, as claimed in each challenged claim, was plainly obvious.

G. Ground 1: Claims 1-25 of the '652 Patent were Obvious Over the LANTUS® 2000 Label and Lougheed

1. Claim 1 was Obvious Over LANTUS® 2000 Label and Lougheed

Claim 1 of the '652 patent recites a "pharmaceutical formulation comprising Gly(A21), Arg(B31), Arg(B32)-human insulin; at least one chemical entity chosen from polysorbate 20 and polysorbate 80; at least one preservative; and water; wherein the pharmaceutical formulation has a pH in the acidic range from 1 to 6.8."

A label for LANTUS® described "Gly(A21), Arg(B31), Arg(B32)-human insulin", or insulin glargine, more than one year before the earliest priority date of the '652 patent. *See* Ex. 1004; Ex. 1003 ¶129. The LANTUS® 2000 Label, which was publicly available to PHOSITAs, *see* Ex. 1004A (December 1, 2000 publication date), taught that "[e]ach milliliter of LANTUS (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection" with a pH of approximately 4.0. Ex. 1004, 1. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. The LANTUS® 2000 Label disclosed

the claim elements of water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus, the LANTUS® 2000 Label taught all the elements recited in claim 1 except "at least one chemical entity chosen from polysorbate 20 and polysorbate 80." *Id.* ¶¶160-62.

Lougheed disclosed and addressed several known issues with insulin formulations, including the propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1 ("Unfortunately, the tendency of insulin to aggregate during storage in and delivery from these devices remains one of the fundamental obstacles to their prolonged clinical use."); Ex. 1003 ¶¶163-69. Lougheed addressed the aggregation issue by comparing different nonionic detergents in extreme storage conditions, and measuring the appearance of aggregated particles through time. Ex. 1006, 1. Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) and polysorbate 80 (*i.e.*, Tween 80), amongst other non-ionic surfactants, showed an enhancement of insulin stability and decrease of aggregate formation. *Id.*, 4, 7 and Table 3; Ex. 1003 ¶¶163-69.

It is not surprising that Lougheed chose polysorbate 20 and polysorbate 80 as an excipient for use in insulin formulations. Polysorbates were commonly used to stabilize other protein and peptide formulations well prior to June 2002, including for commercially-available biologic therapeutics. *See* Jones [Ex. 1016],

3, Table I; Ex. 1003 ¶¶163-69. Moreover, certain polysorbate formulations, including polysorbate 20 and polysorbate 80, were GRAS (Generally Recognized as Safe) and already included in the FDA Inactive Ingredients Guide for various pharmaceutical formulations. Ex. 1003 ¶167. The inclusion of "[p]olysorbate 20 and polysorbate 80, thus, would have been obvious [] to use for inhibiting insulin aggregation." *Id.* ¶172.

In view of at least Lougheed's experiments, the knowledge that polysorbate 20 and polysorbate 80 were generally regarded as effective and safe in inhibiting aggregation in other biologic products, and knowledge of the LANTUS® 2000 Label formulation, a PHOSITA would have had ample reason to add at least nonionic surfactants disclosed in Lougheed, *e.g.*, polysorbate 20 and polysorbate 80, to an insulin glargine formulation, with a reasonable expectation that doing so would successfully inhibit or eliminate insulin's well-known propensity to aggregate. A PHOSITA would especially have had reason because insulin glargine was likely prone to aggregation as monomeric insulin in an acid pH environment. *See id.* ¶¶126, 168. The LANTUS® 2000 Label, in fact, warned users and practitioners not to use the product if aggregation occurred. *See* Ex. 1004, 5-6 ("LANTUS must only be used if the solution is clear and colorless with no particles visible."). Accordingly, a PHOSITA would have had reason, with a reasonable expectation of success, to combine polysorbate 20 or polysorbate 80, as

encouraged by Lougheed [Ex. 1006], with the known and FDA-approved LANTUS® 2000 formulation [Ex. 1004] to inhibit or eliminate insulin aggregation, which was a well-recognized obstacle to the success of insulin as a therapeutic agent.

The use by Lougheed of numerous nonionic surfactants, including the claimed polysorbate 20 and polysorbate 80, to inhibit aggregation and reduce turbidity is simply consistent with the disclosures in the prior art. Ex. 1003 ¶165; *see also* Ex. 1001 3:2-6 ("[I]nsulins, however, show a decreased stability and an increased proneness to aggregation . . . which can make itself felt in the form of turbidity and precipitation (particle formation)."). The '652 patent, which lists a wide range of "partial and fatty acid esters and ethers of polyhydric alcohols" as useful against aggregation of insulin preparations, is thus simply consistent with what the art already knew. A PHOSITA would not have been surprised at the success of combining the known and available insulin glargine formulation with either of two promising aggregation-inhibiting nonionic surfactants to inhibit the formation of particles and the appearance of turbid solutions, would have worked. A PHOSITA would have reasonably expected nothing less. Claim 1 was obvious over the LANTUS® 2000 Label and Lougheed.

2. Independent Claims 7 and 24 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 7 of the '652 patent recites a "pharmaceutical formulation comprising Gly(A21), Arg(B31), Arg(B32)-human insulin, at least one chemical entity chosen from polysorbate and poloxamers; at least one preservative; and water; wherein the pharmaceutical formulation has a pH in the acidic range from 1 to 6.8."

Claim 24 recites a "pharmaceutical formulation comprising Gly(A21), Arg(B31), Arg(B32)-human insulin: at least one chemical entity chosen from polysorbate and poloxamers; at least one preservative chosen from cresol; and water, wherein the pharmaceutical formulation has a pH in the acidic range from 3.5 to 4.5." For the same reasons as for claim 1, claims 7 and 24 were obvious over the LANTUS® 2000 label and Lougheed. *See* Ex. 1003 ¶¶175-80.

"Gly(A21), Arg(B31), Arg(B32)-human insulin", or insulin glargine, was commercially available more than one year before the earliest priority date of the '652 patent as the brand product LANTUS®. The LANTUS® 2000 Label, which was publicly available to PHOSITAs, *see* Ex. 1004A, taught that "[e]ach milliliter of LANTUS (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection" with a pH of approximately 4.0. Ex. 1004, 3. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. The LANTUS® 2000 Label disclosed the claim elements of water and an acidic

pH of approximately 4.0 for the insulin glargine formulation. Thus, as with claim 1, the LANTUS® 2000 Label taught all the elements recited in claims 7 and 24 except "at least one chemical entity chosen from polysorbate and poloxamers."

As above, Lougheed detailed the use of polysorbate 20 and polysorbate 80, *i.e.*, a polysorbate as claimed in claims 7 and 24, as an effective solution to the known propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1; Ex. 1003 ¶¶177-79. Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) and polysorbate 80 (*i.e.*, Tween 80), among other non-ionic surfactants, showed an enhancement of insulin stability and decrease of aggregate formation. Ex. 1006, 4, 7 and Table 3; Ex. 1003 ¶178.

These experiments, knowledge of the safety and efficacy of polysorbate 20 and polysorbate 80 in other commercially-available biological therapeutics and knowledge of the LANTUS® 2000 Label formulation, provided a PHOSITA with ample reason to add at least the nonionic surfactants disclosed in Lougheed, *e.g.*, including the polysorbates polysorbate 20 or polysorbate 80 recited in claims 7 and 24, with a reasonable expectation that doing so would inhibit or eliminate insulin's well-known propensity to aggregate. *See* Ex. 1003 ¶¶175-80. Given insulin glargine's increased propensity for aggregation, and the LANTUS® 2000 Label's warning to not use the product if aggregation occurred, a PHOSITA would have

had specific reason to combine a polysorbate, including polysorbate 20 or polysorbate 80 as encouraged by Lougheed [Ex. 1006], with the known and FDA-approved LANTUS® 2000 formulation [Ex. 1004], with a reasonable expectation of success of inhibiting or eliminating insulin aggregation, a recognized obstacle to the success of insulin as a therapeutic agent. *See* Ex. 1004, 5-6; Ex. 1003 ¶¶175-80. Claims 7 and 24 were obvious over the LANTUS® 2000 Label and Lougheed. *See In re Slayter*, 276 F.2d 408, 411 (C.C.P.A. 1960) ("A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus.").

3. Dependent Claims 2, 8 and 17-19 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 2 of the '652 patent recites that "the at least one chemical entity comprises polysorbate 20." Dependent claim 8 further recites that the polysorbate 20 claimed in claim 2 "is present in an effective amount to avoid turbidity." Dependent claim 17 depends from claim 1, and recites that "the at least one chemical entity is present in a concentration of 5-200 µg/ml." Claim 18 depends from claim 17, and recites that "the at least one chemical entity is present in a concentration of 5-120 µg/ml." Claim 19 depends from claim 18, and further recites that "the at least one chemical entity is present in a concentration of 20-75 µg/ml."

Lougheed detailed the use of polysorbate 20 as an effective solution to the known propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1; Ex. 1003 ¶¶182-84. Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) was one of several nonionic surfactants that showed significant enhancement of insulin stability through inhibition of insulin aggregation, *i.e.*, to avoid turbidity of the formulation. Ex. 1006, 4, 7 and Table 3; Ex. 1003 ¶183.

Moreover, Lougheed also taught the concentration ranges in claims 17, 18 and 19. For example, Lougheed exemplified polysorbate 20 at concentrations of 0.000001% and 0.01% (vol/vol) and polysorbate 80 at concentrations 0.000001%, 0.00001%, 0.01%, and 1% (vol/vol) in the formulations tested. Lougheed [Ex. 1006], 3, Table 3; Ex. 1003 ¶184. Given that the densities of polysorbate 20 and polysorbate 80 are 1.095 g/mL and 1.06 g/mL, respectively, Lougheed thus used polysorbate 20 at concentrations of 0.01095 µg/mL and 109.5 µg/mL, and polysorbate 80 at concentrations of 0.0106 µg/mL, 0.106 µg/mL, 106 µg/mL, and 10600 µg/mL. *See* Ex. 1003 ¶184. Lougheed, thus, disclosed concentrations for polysorbate 20 and polysorbate 80 within the ranges recited in claim 17 and 18.

Lougheed would have suggested the slightly narrowed range of claim 19, which recites "20-75 µg/ml". Not only are the polysorbate 20 and polysorbate 80 levels essentially overlapping with the claimed range, *see Titanium Metals Corp. of*

Am. v. Banner, 778 F.2d 775 (Fed. Cir. 1985), a PHOSITA would have tested and optimized the polysorbate 20 and polysorbate 80 levels taught by Lougheed. Ex. 1003 ¶¶184-85; *see also In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955).

Accordingly, a PHOSITA would have had reason to combine polysorbate 20 (claim 2) as encouraged by Lougheed [Ex. 1006], including at the concentrations tested by Lougheed (claims 17-19), with the known and FDA-approved LANTUS® 2000 formulation [Ex. 1004], with a reasonable expectation of inhibiting or eliminating insulin aggregation, *i.e.*, avoiding turbidity of the formulation (claim 8). Claims 2, 8 and 17-19 were therefore obvious over the Lantus® 2000 Label and Lougheed. Ex. 1003 ¶185.

4. Dependent Claims 3, 4 and 11 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 3 depends from claim 2, and requires that "the at least one preservative is chosen from phenols." Claim 4 depends from claim 3, and recites "wherein the at least one preservative is cresol." Claim 11 depends from claim 1 and recites "wherein the at least one preservative is chosen from phenol, *cresol*, chlorocresol, benzyl alcohol, and parabens." Emphasis added.

The LANTUS® 2000 Label taught an insulin glargine formulation disclosed with "2.7 mg m-cresol". Ex. 1004, 3. Cresol was a known preservative and a derivative of phenol. *See* Ex. 1003 ¶¶98-102. That the LANTUS® 2000 pharmaceutical formulation contained a preservative such as cresol (a phenolic

derivative) is not surprising. Lougheed also investigated the stabilizing effects of phenol and cresol on insulin solutions, finding that both phenol and m-cresol were capable of stabilizing insulin. Ex. 1006, Table 2.

Accordingly, a PHOSITA would have had reason with a reasonable expectation of success to include cresol, as taught by the LANTUS® 2000 Label and as encouraged by Lougheed [Ex. 1006]. Ex. 1003 ¶¶187-89. Claims 3, 4 and 11 were therefore obvious over the Lantus® 2000 Label and Lougheed.

5. Dependent Claim 5 was Obvious Over LANTUS® 2000 Label and Lougheed

Claim 5 depends from claim 4, and recites the formulation "further including zinc."

The LANTUS® 2000 Label taught the inclusion of "30 mcg zinc" in the disclosed insulin glargine formulation. Ex. 1004, 3. Including zinc as a component in the LANTUS® 2000 label was not surprising or inventive. Since the 1950s, zinc has been added to commercial insulin formulations to prolong insulin activity *in vivo*. *See, e.g.*, Hallas-Moller, Diabetes (1956) [Ex. 1017]; Ex. 1003 ¶¶98-102. In fact, various amounts of zinc were tested in insulin glargine formulations well before the earliest priority date of the '652 patent to determine the zinc amounts that would further prolong insulin release and activity. *See* Ex. 1005, 1. A PHOSITA had reason to include zinc, as taught by the LANTUS® 2000

Label, in an insulin pharmaceutical formulation as claimed in claim 5. Ex. 1003 ¶¶191-93.

6. Dependent Claims 6, 12 and 20 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 6 depends from claim 1, and recites "further including at least one isotonicizing agent." Claim 12 depends from claim 6, and recites "wherein the at least one isotonicizing agent is chosen from mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride, and glycerol." Claim 20 depends from claim 12, and recites "wherein at least one isotonicizing agent is chosen from glycerol and mannitol and wherein said at least one isotonicizing agent is present in a concentration of 100-250 mM."

The LANTUS® 2000 Label taught that the disclosed insulin glargine formulation included "20 mg glycerol 85%". Ex. 1004, 3. Accordingly, the LANTUS® 2000 Label taught including glycerol (an isotonicizing agent) in a commercially available insulin glargine formulation. The molecular weight of glycerol is 92.1, so 20 mg glycerol 85% as taught by the LANTUS® 2000 Label is equivalent to 185 mM glycerol, which is within the range as claimed in claim 20. *See* Ex. 1003 ¶197.

Including glycerol, an isotonicizing agent, in the LANTUS® 2000 insulin formulation was neither surprising nor inventive. Isotonicizing (or isotonic) agents, such as glycerol and sodium chloride (NaCl), were routinely added to

parenteral or subcutaneous formulations to prevent cell lysis and attendant pain upon injection. *See* Ex. 1003 ¶¶195-98. Accordingly, it would have been obvious to a PHOSITA that an isotonicizing agent such as glycerol, as taught by the LANTUS® 2000 Label, would be included in an insulin pharmaceutical formulation as claimed in claims 6, 12 and 20.

7. Dependent Claims 9 and 10 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 9 depends from claim 5, and recites "wherein the pharmaceutical formulation has a pH in the acidic range from 3.5 to 6.8." Claim 10 depends from claim 9, and further narrows the pH to an "acidic range from 3.5 to 4.5."

The LANTUS® 2000 Label taught that the insulin glargine was formulated at a pH of approximately 4.0. Ex. 1004, 3. Having a pH of an insulin glargine formulation fall in the pH range recited in claims 9 and 10 is not surprising or inventive. A PHOSITA would have known well before the earliest priority date of the '652 patent that the amino acid substitutions in insulin glargine make it most soluble in an acidic (pH 4.0) environment. *See, e.g.*, Ex. 1005, 1; Ex. 1003 ¶201. Accordingly, it would have been obvious to a PHOSITA that the pH range of an insulin glargine formulation, as taught by the LANTUS® 2000 Label, would be formulated in the range of "from 3.5 to 6.8" (claim 9) or "from 3.5 to 4.5" (claim 10), *i.e.*, an acidic pH environment. Ex. 1003 ¶¶200-02. Claims 9 and 10 were obvious over the LANTUS® 2000 Label and Lougheed.

8. Dependent Claims 13, 14 and 22 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 13 depends from claim 1 and recites that the claimed pharmaceutical formulation "further compris[es] a buffer." Claim 14 depends from claim 13 and recites the buffer as "chosen from TRIS, phosphate, citrate, acetate, and glycylglycine." Claim 22 depends from claim 13 and recites that the "buffer is present in a concentration of 5-250 mM."

Lougheed disclosed the use of non-ionic surfactants and commonly used "salts, buffers and alcohols", including sodium phosphate, sodium bicarbonate with acetic acid and sodium acetate and sodium bicarbonate with sodium phosphate and sodium citrate, in insulin formulations. *See* Lougheed [Ex. 1006], 6, Table 6; Ex. 1003 ¶204. Lougheed specifically taught that of the tested insulin formulations, "[f]ormulations in 25 mM sodium bicarbonate with phosphate-citrate or oxaloacetate buffers demonstrated mildly increased stability with FSRs of 11-20 days". Ex. 1006, 6, Table 6; Ex. 1003 ¶204. The concentration ranges of the sodium bicarbonate, sodium phosphate, acetic acid, sodium acetate and sodium citrate buffers tested fall within the claimed range of 5-250 mM. *See, e.g.*, Ex. 1006, Table 6.

Accordingly, a PHOSITA would have had reason to combine a buffer, including citrate, phosphate and acetate buffers, as encouraged by Lougheed [Ex. 1006], and at the concentrations tested by Lougheed (claim 22), with the known

and FDA-approved LANTUS® 2000 formulation [Ex. 1004] to inhibit or eliminate insulin aggregation with a reasonable expectation of success. Ex. 1003 ¶¶204-06. Claims 13, 14 and 22 were therefore obvious over the LANTUS® 2000 Label and Lougheed.

9. Dependent Claim 21 was Obvious over LANTUS® 2000 Label and Lougheed

Claim 21 depends from claim 1 and recites "wherein NaCl is present in a concentration of up to 150 mM."[4]

Lougheed discloses the testing of commonly used "salts, buffers and alcohols", including sodium chloride at a concentration of 0.9% (equivalent to 154 mM), in insulin formulations, including in combination with sodium dodecyl sulfate (SDS). *See* Lougheed [Ex. 1006], 5-6, Tables 4 and 6; Ex. 1003 ¶208. While the exemplary NaCl concentration is slightly over the claimed range of "up to 150 mM", a PHOSITA would have had reason, with a reasonable expectation of success to combine sodium chloride, as encouraged by Lougheed, with the claimed insulin formulation. The '652 patent provides no evidence of the criticality of the NaCl concentration claimed. *See Aller*, 220 F.2d at 456; accord *Galderma Labs.* 737 F.3d 739 (reversing non-invalidity holding). Moreover, a PHOSITA would

[4] Under a broadest reasonable interpretation, claim 21 includes the formulation components recited in claim 1 and NaCl in the stated concentration range.

have known to reduce the amount of sodium chloride (*i.e.,* lower than 154 mM NaCl) in order to compensate for other components in the formulation. Ex. 1003 ¶209. In light of the known use of NaCl in Lougheed, as well as a deviation from the claimed range within acceptable error standards when making physiological saline solution, Dr. Yalkowsky confirms that neither the '652 patent nor other knowledge in the art would have suggested a concentration change from 154 mM to 150 mM NaCl would have been critical or unobvious. *Id*.

Claim 21 was therefore obvious over the LANTUS® 2000 Label and Lougheed. *Id.* ¶¶208-10.

10. Dependent Claims 15 and 16 were Obvious Over LANTUS® 2000 Label and Lougheed

Claim 15 depends from claim 1 and recites that the "Gly(A21), Arg(B31), Arg(B32)-human insulin is present in a concentration of 60-6000 nmol/ml." Claim 16 depends from claim 15, and further recites "that the Gly(A21), Arg(B31), Arg(B32)-human insulin is present in a concentration of 240-3000 nmol/ml."

The LANTUS® 2000 Label taught "100 IU (3.6378 mg) insulin glargine in the insulin formulation. Ex. 1004, 3. The LANTUS® 2000 Label further provides that insulin glargine (*i.e.*, Gly(A21), Arg(B31), Arg(B32)-human insulin) has a molecular weight of 6063. *Id*. Accordingly, the concentration of insulin glargine taught by the LANTUS® 2000 Label is 600 nmol/mL, which is within the concentration ranges recited in both claims 15 and 16. *See* Ex. 1003 ¶212.

For these reasons, claims 15 and 16 were obvious over the LANTUS® 2000 Label and Lougheed. *Id.* ¶¶212-13.

11. Dependent Claim 23 was Obvious Over LANTUS® 2000 Label and Lougheed

Claim 23 depends from claim 6, and recites "wherein the at least one chemical entity comprises polysorbate 20, at least one preservative is cresol, and the pharmaceutical formulation has a pH in the acidic range from 3.5 to 4.5."

For the same reasons as claims 2, 4 and 10, claim 23 was obvious over the LANTUS® 2000 Label and Lougheed. The LANTUS® 2000 Label included "2.7 mg m-cresol" at a pH of approximately 4.0 for the insulin glargine formulation disclosed. Ex. 1004, 3. Moreover, Lougheed provided a strong reason with a reasonable expectation of success to add polysorbate 20 to improve stability of insulin solutions. *See* Lougheed [Ex. 1006], 1, Table 3; Ex. 1003 ¶¶215-18.

Accordingly, the pharmaceutical formulation of claim 23 would have been obvious over the LANTUS® 2000 Label and Lougheed.

12. Dependent Claim 25 was Obvious Over LANTUS® 2000 Label and Lougheed

Claim 25 depends from claim 1, and recites the formulation "further comprising one or more excipients chosen from acids, alkalis and salts."

The LANTUS® 2000 Label taught preparing an insulin glargine solution and adjusting the pH of the solution to 4.0 using hydrochloric acid and sodium

hydroxide. Ex. 1004, 3; Ex. 1003 ¶220. Moreover, Lougheed further taught the addition of various acids and salts for improving the stability of insulin, including dehydroascorbic acid, hyaluronic acid, n-acetyl neuraminic acid, glutamic acid, sodium chloride, sodium bicarbonate, sodium citrate, and acetic acid, among others. *See* Lougheed [Ex. 1006], Tables 5 and 6; Ex. 1003 ¶220.

Accordingly, in view of the teachings of both the LANTUS® 2000 Label and Lougheed, it would have been obvious and a PHOSITA would have had a reasonable expectation of success of adding an acid, alkali or salt as recited in claim 25 to an insulin formulation. Ex. 1003 ¶¶220-21. Claim 25 was therefore obvious over the LANTUS® 2000 Label and Lougheed.

H. Ground 2: Claims 7 and 24 were Obvious over the LANTUS® 2000 Label and the FASS Insuman Infusat Entry

The limitations of claims 7 and 24 are recited above. *See* §V.B.1, *supra*. The LANTUS® 2000 Label, which was publicly available to PHOSITAs well before the earliest priority date of the '652 patent, *see* Ex. 1004A, taught that "[e]ach milliliter of LANTUS (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection" with a pH of approximately 4.0. Ex. 1004, 3. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. The LANTUS® 2000 Label disclosed the claim elements of water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus,

the LANTUS® 2000 Label taught all the elements recited in claims 7 and 24 except "at least one chemical entity chosen from polysorbate and poloxamers." Ex. 1003 ¶223.

The FASS Insuman Infusat entry disclosed the inclusion of poloxamer poly(oxyethylene, oxypropylene)glycol, *i.e.* "at least one chemical entity chosen from polysorbate and poloxamers" as claimed in claims 7 and 24. *See also* Insuman Infusat Rote Liste entry [Ex. 1033 and 1033A], 6 (inclusion of poloxamer-171 to Insuman Infusat formulation). As noted by the FASS entry, "[a]ddition of a stabilizer poly(oxyethylene, oxypropylene), glycol, prevents precipitation and flocculation of the insulin. This makes INSUMAN INFUSAT particularly suited for use in insulin pumps." *See* Ex. 1007A, 7. PHOSITAs recognized insulin as having a tendency to aggregate during storage and delivery from these devices, *see, e.g.*, Lougheed [Ex. 1006], 1, and that insulin glargine was prone to aggregation issues. Ex. 1003 ¶¶223-29.

Insuman Infusat was commercially available, and established regulatory precedent agency determined that insulin formulations including poloxamer were safe and effective for use in diabetes treatment. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1362-63 (Fed. Cir. 2007) (citing to investor testimony confirming "'part and parcel of pharmaceutically accepted[ ] was to look in pharmacopoeias and compendia' to find an [excipient] having 'precedence for use within the

pharmaceutical industry.'"). This knowledge provided a PHOSITA reason to combine a poloxamer as encouraged by the FASS Insuman Infusat entry [Ex. 1007, 1007A], with the Owens insulin glargine formulation [Ex. 1005], with a reasonable expectation of success of inhibiting or eliminating insulin aggregation, a use specifically recognized for the Insuman Infusat product. *See* Ex. 1005, 3; Ex. 1007, 1007A, 7; Ex. 1003 ¶¶223-29. Claims 7 and 24 were obvious over Owens and the FASS Insuman Infusat entry.

I. Ground 3: Claims 7 and 24 were Obvious over the LANTUS® 2000 Label and Grau

The limitations of claims 7 and 24 are recited above. *See* §V.B.1, *supra*. Moreover, the LANTUS® 2000 Label, which was publicly available to PHOSITAs well before the earliest priority date of the '652 patent, *see* Ex. 1004A, taught the inclusion of cresol as a preservative, water and a pH within the claimed range of 1 to 6.8 (claim 7) or 3.5 to 4.5 (claim 24) in an insulin glargine formulation. Ex. 1004, 3. ("[e]ach milliliter of LANTUS (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection" with a pH of approximately 4.0.). Thus, the LANTUS® 2000 Label taught all the elements recited in claims 7 and 24 except "at least one chemical entity chosen from polysorbate and poloxamers."

Grau disclosed the use of a poloxamer (Genapol) to inhibit insulin aggregation in various test conditions, including with a programmable implantable

medication system (PIMS) which pumped the test formulations into a glass vial at a constant rate throughout the 10+ months of testing, and other *in vivo* and *in vitro* analysis. Ex. 1008, 2-5. Grau found that insulin concentration, chemical stability, and biological potency were maintained when tested both *in vitro* in a shaking platform PIMS rig, as well as *in vivo* in PIMS-implanted dogs. *Id.,* Tables 2-3, 4-5. Grau reported that changes to the poloxamer-containing insulin formulations "were comparable to those seen in insulin stored in a glass vial at 37°C without movement." *Id.*, 4. Grau found that the "[s]urfaces were clean of apparent precipitate even in remote corners." *Id.*, 5. Grau moreover noted that the "[g]lycemic control of [the] diabetic dogs was good … [with] no trend toward either worse diabetic control or increased insulin dosage between refills …". *Id.* Grau concluded that "Genapol, a surface-active polyethylene-propylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces…. The data demonstrate good stability in accelerated laboratory tests and after as long as 5 mo between refills in vivo." *Id.,* 6.

Thus, given insulin glargine's increased propensity for aggregation, and the LANTUS® 2000 Label's warning to not use the product if aggregation occurred, a PHOSITA would have had reason to combine a poloxamer as encouraged by Grau [Ex. 1008], with the known and FDA-approved LANTUS® 2000 formulation [Ex. 1004], with a reasonable expectation of success of inhibiting or eliminating insulin

aggregation, which were a recognized obstacle to the success of insulin as a therapeutic agent. Ex. 1003 ¶¶231-37. Claims 7 and 24 were obvious over the LANTUS® 2000 Label and the Insuman Infusat reference.

J. Ground 4: Claims 1-25 of the '652 Patent were Obvious Over Owens and Lougheed

1. Claim 1 was Obvious Over Owens and Lougheed

The limitations of claim 1 are recited above. *See* §V.B.1, *supra*.

Owens taught insulin glargine (*i.e.*, Gly(A21), Arg(B31), Arg(B32)-human insulin) 1 ml suspension formulations containing "21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin equimolar to 100 U human insulin, together with *m-cresol* and glycerol at pH 4.0," and with 15, 30, or 80 µg/ml zinc (or 2.295, 4.59, and 12.24 µmol/L, respectively). Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶239. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. Owens disclosed the claim elements reciting water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus, Owens taught all the elements recited in claim 1 but for "at least one chemical entity chosen from polysorbate 20 and polysorbate 80."

Lougheed disclosed and addressed several known issues with insulin formulations, including the propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1; Ex. 1003 ¶¶241-43. Lougheed addressed the aggregation issue by comparing different

nonionic detergents in extreme storage conditions and measuring the appearance of aggregated particles over time. *Id.* Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) and polysorbate 80 (*i.e.*, Tween 80), amongst other non-ionic surfactants, showed an enhancement of insulin stability and decrease of aggregate formation. *Id*., 4, 7 and Table 3; Ex. 1003 ¶242. These experiments, and knowledge of the insulin glargine formulation in Owens, provided a PHOSITA with ample reason to add at least the nonionic surfactants disclosed in Lougheed, *e.g.*, including the polysorbates polysorbate 20 or polysorbate 80 recited in claims 7 and 24 of the '652 patent, with a reasonable expectation that doing so would inhibit or eliminate insulin's well-known propensity to aggregate. *See* Ex. 1003 ¶¶239-46. In fact, a PHOSITA would have had specific reason to add the non-ionic surfactants polysorbate 20 (*i.e.*, Tween 20) and polysorbate 80 (*i.e.*, Tween 80) given insulin glargine's increased propensity for aggregation, and the LANTUS® 2000 Label's warning to not use the product if aggregation occurred. *Id.* ¶126. Claim 1 was obvious over Owens and Lougheed.

2. Claims 7 and 24 were Obvious Over Owens and Lougheed

The limitations of claims 7 and 24 are recited above. *See* §V.B.1, *supra*.

Owens recited insulin glargine "together with *m-cresol* and glycerol at pH 4.0," and 15, 30, or 80 µg/ml zinc (or 2.295, 4.59, and 12.24 µmol/L, respectively). Ex. 1005, 815-16 (emphasis added); Ex. 1003 ¶250. Cresol was a known

preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. Owens disclosed the claims elements reciting water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Thus, Owens taught all of the elements recited in claims 7 and 24 but for "at least one chemical entity chosen from polysorbate and poloxamers."

For the same reason as with claim 1, Lougheed in combination with Owens obviates claims 7 and 24. Lougheed detailed the use of polysorbate 20 and polysorbate 80 as an effective solution to the known propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1; Ex. 1003 ¶¶251-52. Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) and polysorbate 80 (*i.e.*, Tween 80), amongst other non-ionic surfactants, showed an enhancement of insulin stability and decrease of aggregate formation. *Id*., 427, 430 and Table 3; Ex. 1003 ¶252.

These experiments, and knowledge of the insulin glargine formulation in Owens, provided a PHOSITA with ample reason to add at least the nonionic surfactants disclosed in Lougheed, *e.g.*, polysorbate 20 or polysorbate 80 recited in claims 7 and 24 of the '652 patent, with a reasonable expectation that doing so would inhibit or eliminate insulin's well-known propensity to aggregate. *See* Ex. 1003 ¶¶249-53. Given insulin glargine's increased propensity for aggregation, and the LANTUS® 2000 Label's warning to not use the product if aggregation

occurred, a PHOSITA would have had specific reasons to do so. *Id.* ¶126. Claims 7 and 24 were obvious over Owens and Lougheed.

3. Dependent Claims 2, 8 and 17-19 were Obvious Over Owens and Lougheed

The limitations and dependencies of claims 2, 8 and 17-19 are presented above. *See* §V.B.1, *supra*.

Lougheed detailed the use of polysorbate 20 as an effective solution to the known propensity for insulin to aggregate upon storage and delivery in injection devices and infusion pumps. *See* Lougheed [Ex. 1006], 1; Ex. 1003 ¶¶255-57. Lougheed specifically taught that polysorbate 20 (*i.e.*, Tween 20) was one of several nonionic surfactants that showed significant enhancement of insulin stability through inhibition of insulin aggregation, *i.e.*, to avoid turbidity of the formulation. Ex. 1006, 4, 7, Table 3; Ex. 1003 ¶256; Ex. 1001, 3:2-6 ("[I]nsulins, however, show a decreased stability and an increased proneness to aggregation . . . which can make itself felt in the form of turbidity and precipitation (particle formation).").

Moreover, Lougheed also taught the concentration ranges in claims 17, 18 and 19. For example, Lougheed exemplified polysorbate 20 at concentrations of 0.000001% and 0.01% (vol/vol) and polysorbate 80 at concentrations 0.000001%, 0.00001%, 0.01%, and 1% (vol/vol) in the formulations tested. Ex. 1006, Table 3; Ex. 1003 ¶257. Given that the densities of polysorbate 20 and polysorbate 80 are

1.095 g/mL and 1.06 g/mL, respectively, Lougheed thus used polysorbate 20 at concentrations of 0.01095 µg/mL and 109.5 µg/mL, and polysorbate 80 at concentrations of 0.0106 µg/mL, 0.106 µg/mL, 106 µg/mL, and 10600 µg/mL. *See* Ex. 1003 ¶257. Each of these concentrations for polysorbate 20 and polysorbate 80 are within the ranges recited in claims 17 and 18.

The slightly narrowed range of claim 19, which recites "20-75 µg/ml" was obvious from Lougheed's teaching. Not only are the polysorbate 20 and polysorbate 80 levels essentially overlapping with the claimed range, *see Titanium Metals*, 778 F.2d 775 (close amounts suggest prima facie obviousness), a PHOSITA would have had reason to test and optimize the polysorbate 20 and polysorbate 80 levels taught by Lougheed. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (optimization is routine); *In re Ethicon, Inc.*, 844 F.3d 1344 (Fed. Cir. 2017); Ex. 1003 ¶ 257; *see also Aller*, 220 F.2d at 456; *Galderma Labs.*, 737 F.3d at 739.

A PHOSITA would have had reason to combine polysorbate 20 (claim 2) as encouraged by Lougheed [Ex. 1006], including at the concentrations Lougheed tested (claims 17-19), with the insulin glargine formulation Owens disclosed [Ex. 1005] to inhibit or eliminate insulin aggregation, *i.e.* avoid turbidity of the formulation (claim 8), with a reasonable expectation of success. Ex. 1003 ¶¶255-57; *see also* Ex. 1001 3:2-6 ("[I]nsulins, however, show a decreased stability and

an increased proneness to aggregation . . . which can make itself felt in the form of turbidity and precipitation (particle formation).”). Claims 2, 8 and 17-19 were obvious over Owens and Lougheed.

4. Dependent Claims 3, 4 and 11 were Obvious Over Owens and Lougheed

The limitations and dependencies of claims 3, 4 and 11 are presented above. *See* §V.B.1, *supra*.

Owens taught insulin glargine suspension formulations containing *m-cresol*. Ex. 1005, 3-4; Ex. 1003 ¶260. Cresol was a known preservative and a derivative of phenol, which was known by PHOSITAs at the time. *See* Ex. 1003 ¶¶98-102.

Owen’s insulin glargine pharmaceutical formulation containing a preservative such as cresol (a phenolic derivative) is not surprising. Lougheed investigated the stabilizing effects of phenol and cresol on insulin solutions, finding that both phenol and m-cresol successfully stabilized insulin. Ex. 1006, Table 2.

A PHOSITA had reason to include cresol (a preservative and phenol derivative), as Owens taught and Lougheed encouraged, with a reasonable expectation of success. Ex. 1003 ¶¶260-61. Claims 3, 4 and 11 were obvious over the Owens and Lougheed.

5. Dependent Claim 5 was Obvious Over Owens and Lougheed

The language of claim 5 is presented above. *See* §V.B.1, *supra*.

Owens taught insulin glargine suspension formulations containing 15, 30, or 80 µg/ml zinc (or 2.295, 4.59, and 12.24 µmol/L, respectively). Ex. 1005, 3-4; Ex. 1003 ¶264.

Owen's inclusion of zinc in insulin glargine formulations was not surprising or inventive. Since the 1950s, zinc has been added to commercial insulin formulations to prolong insulin activity *in vivo*. *See, e.g.*, Hallas-Moller [Ex. 1017]; Ex. 1003 ¶265. Owens tested the various amounts of zinc to determine the zinc amounts that would further prolong insulin release and activity. *See* Ex. 1005, 1. Accordingly, it would have been obvious to a PHOSITA that zinc, as taught by Owens, would be included in an insulin pharmaceutical formulation as claimed in claim 5. Ex. 1003 ¶¶264-66.

6. Dependent Claims 6, 12 and 20 were Obvious Over Owens and Lougheed

The limitations of claims 6, 12 and 20 are presented above. *See* §V.B.1, *supra*.

Owens taught insulin glargine suspension formulations containing "… *glycerol* at pH 4.0." Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶268.

Owen's inclusion of glycerol, an isotonicizing agent, in the insulin glargine formulation was not surprising or inventive. Isotonicizing (or isotonic) agents, such as glycerol, are routinely added to parenteral or subcutaneous formulations to

prevent cell lysis and attendant pain upon injection. *See* Ex. 1003 ¶269. Moreover, Lougheed disclosed the use of 1.6% glycerol in an insulin formulation. *See* Ex. 1006, 7, Table 2. A PHOSITA had ample reason to include an isotonicizing agent such as glycerol, as Owens taught, in an insulin glargine pharmaceutical formulation as claimed in claims 6 and 12. Ex. 1003 ¶¶268-71.

7. Dependent Claims 9 and 10 were Obvious Over Owens and Lougheed

The limitations of claims 9 and 10 are presented above. *See* §V.B.1, *supra*.

Owens taught insulin glargine suspension formulations "… at pH 4.0.". Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶273. It is not surprising or inventive that the pH of an insulin glargine formulation would fall in the pH range recited in claims 9 and 10. A PHOSITA would have known that because of the amino acid substitutions in insulin glargine, insulin glargine is most soluble in an acidic (pH 4.0) environment. *See, e.g.*, Ex. 1005, 1; Ex. 1003 ¶¶274-75. A PHOSITA knew that the pH range of an insulin glargine formulation, as Owens taught, would fall in the range of "from 3.5 to 6.8" (claim 9) or "from 3.5 to 4.5" (claim 10). Claims 9 and 10 were obvious over Owens and Lougheed.

8. Dependent Claims 13, 14 and 22 were Obvious Over Owens and Lougheed

The limitations of claims 13, 14 and 22 are presented above. *See* §V.B.1, *supra*.

Lougheed detailed not only the use of non-ionic surfactants, but also commonly used "salts, buffers and alcohols", including sodium phosphate, sodium bicarbonate with acetic acid and sodium acetate and sodium bicarbonate with sodium phosphate and sodium citrate buffers, in insulin formulations. *See* Ex. 1006, 6, Table 6; Ex. 1003 ¶277. Lougheed specifically taught that "[f]ormulations in 25 mM sodium bicarbonate with phosphate-citrate or oxaloacetate buffers demonstrated mildly increased stability with FSRs of 11-20 days" of the tested insulin formulations. Ex. 1006, 6, Table 6; Ex. 1003 ¶277-78. The concentration ranges of the sodium bicarbonate, sodium phosphate, acetic acid, sodium acetate and sodium citrate buffers tested all fall within the claimed range of 5-250 mM. Ex. 1006, Table 6, ranging from 20 mM to 100 mM (sodium phosphate).

A PHOSITA had reason, with a reasonable expectation of success, to combine a buffer, including citrate, phosphate and acetate buffers, as Lougheed encouraged, including at the concentrations Lougheed tested (claim 22), with Owens [Ex. 1005] to inhibit or eliminate insulin aggregation. Ex. 1003 ¶¶277-79. Claims 13, 14 and 22 were obvious over Owens and Lougheed.

9. Dependent Claim 21 was Obvious Over Owens and Lougheed

The limitations of claim 21 are presented above. *See* §V.B.1, *supra*.

Lougheed discloses the testing of commonly used "salts, buffers and alcohols", including sodium chloride at a concentration of 0.9% (equivalent to 154

mM), in insulin formulations, including in combination with sodium dodecyl sulfate (SDS). *See* Ex. 1006, 5-6, Tables 4 and 6; Ex. 1003 ¶285. While the exemplary NaCl concentration is slightly over the claimed range of "up to 150 mM", a PHOSITA would have had reason, with a reasonable expectation of success to combine sodium chloride, as encouraged by Lougheed, with the claimed insulin formulation. The '652 patent provides no evidence of the criticality of the NaCl concentration claimed. *See Aller*, 220 F.2d at 456; accord *Galderma Labs.*, 737 F.3d at 739 (reversing non-invalidity holding). In light of the common use of physiological saline (0.9% or 154 mM), as well as a deviation from the claimed range within acceptable error standards when making physiological saline solution, Dr. Yalkowsky confirms that neither the '652 patent nor other knowledge in the art would have suggested a concentration change from 154 mM to 150 mM NaCl would have been critical. Ex. 1003 ¶¶285-87.

Claim 21 was therefore obvious over Owens and Lougheed.

10. Dependent Claims 15 and 16 were Obvious Over Owens and Lougheed

The limitations of claims 15 and 16 are presented above. *See* §V.B.1, *supra*.

Owens taught insulin glargine formulations containing "21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin equimolar to 100 U human insulin ...." Ex. 1005, 3-4; Ex. 1003 ¶290. A PHOSITA would have known that insulin glargine has a molecular weight of 6063, and that 100 U of insulin glargine is equivalent to about

3.6 mg insulin glargine per mL. Ex. 1003 ¶¶289-92. Accordingly, a PHOSITA would recognize that 100 U of insulin glargine is equivalent to 600 nmol/mL, which is within the concentration ranges recited in both claims 15 and 16.

For these reasons, claims 15 and 16 were obvious over Owens and Lougheed.

11. Dependent Claim 23 was Obvious Over Owens and Lougheed

The limitation of claim 23 is presented above. *See* §V.B.1, *supra*.

For the same reasons as claims 2, 4, 6 and 10, claim 23 was obvious over Owens and Lougheed. Owens taught insulin glargine suspension formulations containing "*m-cresol* and glycerol at *pH 4.0*." Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶290. Moreover, Lougheed provided a strong reason with a reasonable expectation of success to add polysorbate 20 to an insulin glargine formulation to improve the stability of insulin solutions. *See* Ex. 1006, 1, Table 3; Ex. 1003 ¶¶289-92.

Accordingly, the pharmaceutical formulation of claim 23 would have been obvious over Owens and Lougheed.

12. Dependent Claim 25 was Obvious Over Owens and Lougheed

The limitation of claim 25 is presented above. *See* §V.B.1, *supra*.

Adjusting the pH using hydrochloric acid and sodium hydroxide, a standard procedure recognized by any PHOSITA, is explicitly disclosed by Lougheed. *See* Ex. 1006, 2. Moreover, Lougheed taught the addition of various acids and salts for improving the stability of insulin, including dehydroascorbic acid, hyaluronic acid, n-acetyl neuraminic acid, glutamic acid, sodium chloride, sodium bicarbonate, sodium citrate, and acetic acid, among others. *See id.,* Tables 5 and 6; Ex. 1003 ¶¶294-95.

Accordingly, in view of the teachings of both Owens and Lougheed, it would have been obvious and a PHOSITA would have had a reasonable expectation of success of adding an acid, alkali or salt as recited in claim 25 to an insulin glargine formulation. Claim 25 was obvious Owens and Lougheed.

K. Ground 5: Claims 7 and 24 were Obvious over Owens and the Insuman Infusat Reference

The limitations of claims 7 and 24 are recited above. *See* §V.B.1, *supra*. Moreover, as above, Owens taught insulin glargine (*i.e.*, Gly(A21), Arg(B31), Arg(B32)-human insulin) 1 ml suspension formulations containing "21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin equimolar to 100 U human insulin, together with *m-cresol* and glycerol at pH 4.0," and with 15, 30, or 80 µg/ml zinc (or 2.295, 4.59, and 12.24 µmol/L, respectively). Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶297. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102, 297; Ex. 1001, 4:27-28. Owens disclosed the claimed elements of water and

an acidic pH of approximately 4.0 for the insulin glargine formulation. Ex. 1005, 3. Thus, Owens taught all the elements recited in claims 7 and 24 except "at least one chemical entity chosen from polysorbate and poloxamers."

The FASS Insuman Infusat entry disclosed the inclusion of poloxamer poly(oxyethylene, oxypropylene)glycol, *i.e.* "at least one chemical entity chosen from polysorbate and poloxamers" as claimed in claims 7 and 24. *See also,* Insuman Infusat Rote Liste entry [Ex. 1033 and 1033A], 6 (inclusion of poloxamer-171 to Insuman Infusat formulation); Ex. 1003, ¶¶298-99. As noted by the FASS entry, "[a]ddition of a stabilizer poly(oxyethylene, oxypropylene), glycol, prevents precipitation and flocculation of the insulin. This makes INSUMAN INFUSAT particularly suited for use in insulin pumps…" *See* Ex. 1007A, 7. PHOSITAs recognized insulin as having a tendency to aggregate during storage and delivery from these devices, *see, e.g.*, Lougheed [Ex. 1006], 1, and that insulin glargine was prone to aggregation issues. Ex. 1003 ¶299.

Insuman Infusat was commercially available, and established regulatory precedent agency determined that insulin formulations including poloxamer were safe and effective for use in diabetes treatment. *See Pfizer*, 480 F.3d at 1362-63 (citing to investor testimony confirming "'part and parcel of pharmaceutically accepted[ ] was to look in pharmacopoeias and compendia' to find an [excipient] having 'precedence for use within the pharmaceutical industry.'"). This knowledge

provided a PHOSITA reason to combine a poloxamer as encouraged by the FASS Insuman Infusat entry [Ex. 1007, 1007A], with the Owens insulin glargine formulation [Ex. 1005], with a reasonable expectation of success of inhibiting or eliminating insulin aggregation, a use specifically recognized for the Insuman Infusat product. *See* Ex. 1005, 3; Ex. 1007A, 7; Ex. 1003 ¶¶297-300. Claims 7 and 24 were obvious over Owens and the FASS Insuman Infusat entry.

L. Ground 6: Claims 7 and 24 were Obvious over Owens and Grau

The limitations of claims 7 and 24 are recited above. *See* §V.B.1, *supra*. Moreover, as above, Owens taught insulin glargine (*i.e.*, Gly(A21), Arg(B31), Arg(B32)-human insulin) 1 ml suspension formulations containing "21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin equimolar to 100 U human insulin, together with *m-cresol* and glycerol at pH 4.0," and with 15, 30, or 80 µg/ml zinc (or 2.295, 4.59, and 12.24 µmol/L, respectively). Ex. 1005, 3-4 (emphasis added); Ex. 1003 ¶303. Cresol was a known preservative, as the '652 patent confirms. *See* Ex. 1003 ¶¶98-102; Ex. 1001, 4:27-28. Owens disclosed the claims elements of water and an acidic pH of approximately 4.0 for the insulin glargine formulation. Ex. 1005, 3. Thus, Owens taught all the elements recited in claims 7 and 24 except "at least one chemical entity chosen from polysorbate and poloxamers."

Grau disclosed the use of a poloxamer (Genapol) to inhibit insulin aggregation in various test conditions, including with a programmable implantable

medication system (PIMS) which pumped the test formulations into a glass vial at a constant rate throughout the 10+months of testing, as well as other *in vivo* and *in vitro* analysis. Ex. 1008, 2-5; Ex. 1003 ¶¶304-05. Grau found that insulin concentration, chemical stability, and biological potency were maintained when tested both *in vitro* in a shaking platform PIMS rig, as well as *in vivo* in PIMS-implanted dogs. *See, e.g.*, Ex. 1008, Tables 2-3 and 4-5. Grau reported that changes to the poloxamer-containing insulin formulations "were comparable to those seen in insulin stored in a glass vial at 37°C without movement." *Id.,* 4. Grau found that the "[s]urfaces were clean of apparent precipitate even in remote corners." *Id.,* 5. Grau moreover noted that the "[g]lycemic control of [the] diabetic dogs was good … [with] no trend toward either worse diabetic control or increased insulin dosage between refills …". *Id.* Grau concluded that "Genapol, a surface-active polyethylene-propylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces…. The data demonstrate good stability in accelerated laboratory tests and after as long as 5 mo between refills in vivo." *Id.,* 6.

From Grau's work, and with knowledge of Owen's base insulin glargine formulation, a PHOSITA had reason to add at least the poloxamer disclosed in Grau as claimed in claims 7 and 24, to inhibit or eliminate insulin's well-known propensity to aggregate with a reasonable expectation of success. *See* Ex. 1003 ¶¶302-06. A PHOSITA would have had reason, with a reasonable expectation of

success to combine a poloxamer as encouraged by Grau [Ex. 1008], with the Owens formulation [Ex. 1005] to inhibit or eliminate insulin aggregation issues, a recognized obstacle to the success of insulin as a therapeutic agent. Claims 7 and 24 were therefore obvious over Owens and Grau.

M. Secondary Considerations Cannot Preclude Obviousness.

Although the patentee may offer secondary considerations of nonobviousness, any such evidence would be "insufficient" to "overcome the strong [case] of obviousness" here. *Pfizer,* 480 F.3d at 1372. Sanofi-Aventis has the burden of production for any evidence of patentability. *Id.,* 1360. Mylan nonetheless preliminarily addresses some positions Sanofi-Aventis might take.

1. Addition of a Nonionic Surfactant as Recited in the '652 Patent Was Completely Expected

While the '652 patent claims that it "surprisingly found that the addition of surfactants can greatly increase the stability of acidic insulin preparations," Sanofi-Aventis' surprise was unfounded. Not only did the prior art disclose tests with species within the broadly claimed polysorbates and poloxamers disclosed in the '652 patent, the '652 patent in experimental examples used the same two polysorbates: polysorbate 20 (Tween 20) and polysorbate 80 (Tween 80), that worked in the prior art. *See* Ex. 1006; Ex. 1003 ¶503. Sanofi-Aventis cannot reasonably assert that the addition of surfactant to the known and available prior art LANTUS® 2000 insulin glargine formulations achieved any unexpected result. Ex.

1003 ¶503. On the contrary, it was entirely expected that the addition of nonionic surfactants as claimed in the '652 patent would have worked, as shown by the prior art. *In re Skoll*, 523 F.2d 1392, 1397 (C.C.P.A. 1975) (expected results indicate obviousness). Similarly, there is no evidence of record of a long-felt need, failure of others or industry acclaim for an insulin glargine formulation with a polysorbate or poloxamer. *Id.* ¶¶504-08.

2. Copying By Generic Drug Makers Is Irrelevant.

If Sanofi-Aventis argues that Mylan and other generic drug companies seek to copy the invention of the '652 patent by commercializing generic versions of insulin glargine, this would fail to support non-obviousness. Copying "is required for FDA approval" of generic drugs, any "evidence of copying in the [generic drug] context is not probative of nonobviousness." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

Dated: June 5, 2017

/Jeffrey W. Guise/

Jeffrey W. Guise, Ph.D.
Lead Counsel
Reg. No. 34,613
Wilson Sonsini Goodrich & Rosati PC
650 Page Mill Road
Palo Alto, CA 94304
Telephone: (858) 350-2225
Facsimile: (650) 493-6811
E-mail: jguise@wsgr.com

CERTIFICATION UNDER 37 C.F.R. §42.24(d)

Under the provisions of 37 C.F.R. §42.24(d), the undersigned hereby certifies that the word count for the foregoing Petition for Inter Partes Review totals 13,028, which is less than the 14,000 allowed under 37 C.F.R. 42.24(a)(i). In accordance with 37 C.F.R. 42.24(a), this word count does not include table of contents, table of authorities, mandatory notices under §42.8, certificate of service or word count, or appendix of exhibits or claim listing.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,476,652 and Exhibits 1001-1035** by *Federal Express Next Business Day Delivery* on this day, June 5, 2017 on the Patent Owner's correspondence address of record for the subject patent as follows:

AVENTIS PHARMA
DEUTSCHLAND GMBH
INDUSTRIEPARK
HOCHST/BUILDING K801
FRANKFURT AM, 65926
GERMANY

ANDREA Q. RYAN
SANOFI
55 Corporate Drive
MAIL CODE: 55A-505A
BRIDGEWATER NJ 08807

Respectfully submitted,

Dated: June 5, 2017

/Jeffrey W. Guise/
Jeffrey W. Guise, Ph.D.,
Lead Counsel
Reg. No. 34,613

Wilson Sonsini Goodrich & Rosati PC
650 Page Mill Road
Palo Alto, CA 94304
Telephone: (858) 350-2225
Facsimile: (650) 493-6811
E-mail: jguise@wsgr.com

EXHIBIT 4

Trials@uspto.gov
571-272-7822

Paper No. 13
Entered: December 13, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Patent Owner.

Case IPR2017-01526
Patent 7,476,652 B2

Before ERICA A. FRANKLIN, ROBERT A. POLLOCK, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges.*

ANKENBRAND, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Mylan Pharmaceuticals, Inc. ("Petitioner") requests an *inter partes* review of claims 1–25 of U.S. Patent No. 7,476,652 B2 (Ex. 1001, "the '652 patent"). Paper 2 ("Pet."). Sanofi-Aventis Deutschland GmbH ("Patent Owner") filed a Preliminary Response. Paper 8 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Applying that standard, and upon consideration of the information presented in each Petition and Preliminary Response, we institute an *inter partes* review as to claims 1–25 of the '652 patent.

II. BACKGROUND

A. Related Matters

Patent Owner identifies the following pending litigation involving the '652 patent: *Sanofi-Aventis U.S. LLC v. Merck Sharp & Dohme Corp.*, C.A. No. 1-16-cv-00812-RGA (D. Del.); *Sanofi-Aventis v. Merck Sharp & Dohme Corp.*, C.A. No. 2-17-cv-05914 (D.N.J.). Paper 7, 2. Patent Owner also identifies the following concluded litigation involving the '652 patent: *Sanofi-Aventis U.S. LLC v. Eli Lilly & Co.*, C.A. No. 1-14-cv-00113-RGA (D. Del.); *Sanofi-Aventis U.S. LLC v. Eli Lilly & Co.*, C.A. No. 1-14-cv-00884-RGA (D. Del.). *Id.*; Prelim. Resp. 51–52. Patent Owner also identifies as related IPR201-01528— an *inter partes* review Petitioner filed challenging U.S. Patent No. 7,713,930 (Ex. 1002, "the '930 patent"), which issued from continuation application to the application that issued as the '652 patent. Paper 7, 2.

As Patent Owner points out, the Petition does not identify the pending or concluded litigation involving the '652 patent. Prelim. Resp. 51–52. In that regard, the Petition states that Petitioner "is not a party to any litigation related to the '652 patent." Pet. 2. Patent Owner argues that we should deny the Petition due to Petitioner's failure to identify all related matters pursuant to 37 C.F.R. § 42.8(b)(2). Prelim. Resp. 51–52.

We do not find sufficient grounds to deny the Petition on that basis. To be sure, § 42.8(b)(2) requires parties to identify "any other judicial or administrative matter that would affect, or be affected by, a decision in the proceeding." The district court litigation that Patent Owner identifies, however, does not involve Petitioner as a party, and it is not apparent from the record that Petitioner was aware of, but failed to identify, that district court litigation.

Although we do not deny the Petition as Patent Owner requests, we direct Petitioner to update its mandatory notices, within three days of the entry of this Decision, to include the pending and concluded litigation that Patent Owner identifies, as well as IPR2017-01528. We also remind the parties of their continuing obligation to file an updated mandatory notice "within 21 days of a change of the information" required in the notices. 37 C.F.R. § 42.8(a)(3).

B. The '652 Patent (Ex. 1001)

The '652 patent, titled "Acidic Insulin Preparations Having Improved Stability," issued on January 13, 2009. Ex. 1001, (45), (54). The '652 patent relates to pharmaceutical formulations comprising a modified insulin—insulin glargine (Gly(A21)-Arg(B31)-Arg(B32)-human insulin) —and at least one surfactant. *See, e.g.*, Ex. 1001, Abstract, 1:11–19, 11:2–9. The formulation is used to treat diabetes, and is "particularly suitable for preparations in which a high stability to thermal and/or physicomechanical stress is necessary." *Id.* at 1:19–22.

According to the specification, insulin glargine was a known modified insulin with a prolonged duration of action injected once daily as an acidic, clear solution that "precipitates on account of its solution properties in the physiological pH range of the subcutaneous tissue as a stable hexamer associate." *Id.* at 2:56–61.

The specification explains that, at acidic pH, insulins exhibit decreased stability and increased susceptibility to aggregation in response to thermal and physicomechanical stress, resulting in turbidity and precipitation (i.e., particle formation). *Id.* at 3:2–6. Such stresses can arise during use or shaking of the insulin solution. *Id.* at 5:34–56. Also contributing to aggregation are hydrophobic surfaces with which the insulin solution comes into contact, including those on glass vessels storing the insulin solution, sealing cap stopper materials, and siliconized insulin syringes. *Id.* at 3:8–17.

According to the specification, the applicants "surprisingly [] found" that adding surfactants to the insulin solution or formulation "can greatly increase the stability of acidic insulin preparations," thereby producing insulin solutions with "superior stability to hydrophobic aggregation nuclei for several months [u]nder temperature stress." *Id.* at 3:41–45; *see id.* at 5:20–10:67 (examples showing that adding the surfactant polysorbate 20 or polysorbate 80 to an insulin glargine formulation stabilizes the formulation in use and during physicomechanical stressing).

C. Illustrative Claim

Petitioner challenges claims 1–25 of the '652 patent, of which claims 1, 7, and 24 are independent. Claim 1 of the '652 patent is illustrative of the claimed subject matter and recites:

> 1. A pharmaceutical formulation comprising Gly(A21), Arg(B31), Arg(B32)-human insulin;

> at least one chemical entity chosen from polysorbate 20 and polysorbate 80;
>
> at least one preservative; and
>
> water,
>
> wherein the pharmaceutical formulation has a pH in the acidic range from 1 to 6.8.

Ex. 1001, 11:2–9.

D. The Asserted Grounds of Unpatentability

Petitioner asserts that the challenged claims of the '652 patent are unpatentable based on the following grounds:

References	Statutory Basis	Claims Challenged
Lantus Label[1] and Lougheed[2]	§ 103	1–25
Lantus Label and FASS[3]	§ 103	7, 24
Lantus Label and Grau[4]	§ 103	7, 24
Owens[5] and Lougheed	§ 103	1–25
Owens and FASS	§ 103	7, 24
Owens and Grau	§ 103	7, 24

[1] Physicians' Desk Reference, Lantus entry 709–713 (55th ed. 2001) (Ex. 1004). We refer in this decision to the corrected version of Exhibit 1004.

[2] W.D. Lougheed et al., *Physical Stability of Insulin Formulations*, 32 DIABETES 424–432 (1983) (Ex. 1006).

[3] Farmaceutiska Specialiteter I Sverige ("FASS"), Summary of Product Characteristics Entry for Insuman Infusat (2000) (certified English translation provided as Ex. 1007A; original Swedish version provided as Ex. 1007).

[4] Ulrich Grau & Christopher D. Saudek, *Stable Insulin Preparation for Implanted Insulin Pumps – Laboratory & Animal Trials*, 36 DIABETES 1453–59 (1987) (Ex. 1008).

[5] David R. Owens et al., *Pharmacokinetics of ^{125}I-Labeled Insulin Glargine (HOE 901) in Healthy Men – Comparison with NPH insulin and the influence of different subcutaneous injection sites*, 23 DIABETES CARE 813–819 (2000) (Ex. 1005).

Petitioner supports the Petition with the testimony of Samuel H. Yalkowsky, Ph.D. (Ex. 1003).

III. ANALYSIS

A. Discretionary Denial under 35 U.S.C. § 325(d)

Patent Owner argues that we should exercise our discretion to deny all of the asserted grounds under 35 U.S.C. § 325(d) because they present substantially the same prior art and arguments the Office previously considered during the prosecution of the '652 patent. Prelim. Resp. 43–48. Patent Owner points to the Examiner's rejection over a combination of art that included Dörschug[6]—a patent that discloses a plasmid for preparing insulin glargine and various formulation components in aqueous solution. *Id.* at 44. Patent Owner contends that the list of components Dörschug discloses "substantially overlaps with the list of components that Petitioner asserts" Lantus Label and Owens teach. *Id.* Patent Owner also points to several patents disclosing surfactants in formulations of human or animal insulins that the Examiner considered during prosecution of the '652 patent—Massey[7] and Hirai.[8] *Id.* at 44–46 (citing Ex. 1001A,[9] 2406–11; Ex. 1023; Ex. 1024). Patent Owner asserts that the Office, therefore, "previously considered the patentability of the challenged claims over Glargine and non-Glargine insulin art, and concluded that the claimed Glargine formulation would not have been obvious." *Id.* at 46.

[6] Dörschug, U.S. Patent No. 5,656,277, issued Aug. 12, 1997 (Ex. 2004).
[7] Massey et al., U.S. Patent No. 4,839,341, issued June 13, 1989 (Ex. 1024).
[8] Hirai et al., U.S. Patent No. 4,153,689, issued May 8, 1979 (Ex. 1023).
[9] Exhibit 1001A is the prosecution history of the '652 patent. For ease of reference, we refer to the pagination that Petitioner has added to the exhibit.

We have considered Patent Owner's arguments, but decline to exercise our discretion under § 325(d). First, we note that Petitioner's asserted references are not the same references that the Examiner considered during prosecution. *See* Pet. 14 (explaining that the Examiner's rejections did not include Lantus Label, Owens, Lougheed, FASS, or Grau).

Second, even assuming that the art Petitioner asserts is substantially similar to the art that the Office considered during prosecution of the '652 patent, Patent Owner directs us to references that the Examiner considered at different stages of prosecution and in making rejections over claims differing in scope than the issued claims. That is, the Examiner did not reject the claims of the '652 patent over the combination of Dörschug, Massey, and Hirai, or any combination of those references. Rather, the Examiner rejected the applicants' originally-filed claims as anticipated or obvious over Massey, and as anticipated or obvious over Hirai, among other rejections. *See* Ex. 1001A, 2407–09. At a later stage of prosecution—after the applicants canceled the original claims, presented new claims, and made amendments to those new claims—the Examiner rejected the amended claims as obvious over a combination including Dörschug, but not Massey and/or Hirai. *Id.* at 187, 190–191.

Further, although Patent Owner cites to Dörschug's disclosure of a plasmid for the preparation of insulin glargine and components in aqueous solution, we are not aware of any rejection in which the Examiner relied on Dörschug as teaching insulin glargine in a formulation with particular excipients (i.e., the arguments Petitioner asserts with respect to Lantus Label and Owens). Rather, the Examiner relied on Dörschug as teaching insulin glargine in weakly acidic solution. *See, e.g.*, Ex. 1001A, 55, 191. For these reasons, we decline to exercise our discretion to deny institution under § 325(d).

B. Level of Ordinary Skill in the Art

We consider each asserted ground of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends that, as of June 2002, a person of ordinary skill in the art would have had "an M.S. or Ph.D. or equivalent in pharmacology, pharmaceutical sciences, or a closely related field; or an M.D. with practical academic or industrial experience in peptide injection formulations or stabilizing agents for such formulations." Pet. 14 (citing Ex. 1003 ¶¶ 31–34). As an example, Petitioner notes that a person of ordinary skill in the art would have had experience in surfactants that are commonly used in peptide injection formulations and an understanding of the factors that contribute to the molecule's instability. *Id.*; Ex. 1003 ¶ 33. Petitioner further contends that an ordinary artisan may have "consulted with one or more team members of experienced professionals to develop an insulin formulation resistant to the well-known aggregation propensities of insulin molecules." Pet. 14–15; *see* Ex. 1003 ¶ 34.

At this stage of the proceeding, Patent Owner does not dispute Petitioner's proposed level of ordinary skill, which we adopt for purposes of this decision. *See* Prelim. Resp. 11. We also find, for purposes of this decision, that the prior art itself is sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect the appropriate level of ordinary skill in art). Further, based on Dr. Yalkowsky's statement of qualifications and curriculum vitae, for the purposes of this decision, we find that he is qualified to opine from the perspective of a person of ordinary skill in the art at the time of the invention. *See* Ex. 1003 ¶¶ 2–16 (Dr. Yalkowsky's statement of qualifications); *id.* at Exhibit A (Dr. Yalkowsky's curriculum vitae).

C. Claim Construction

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, claim terms are given their ordinary and customary meaning in view of the specification, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner proposes that we construe several claim limitations, including the phrase "a pharmaceutical formulation," and the terms "polysorbate," "poloxamer," "polysorbate 20," and "polysorbate 80." Pet. 15–17. Although Patent Owner does not dispute Petitioner's proposed constructions at this stage of the proceeding (*see* Prelim. Resp. 11), neither party identifies a dispute that turns on the meaning of the limitations Petitioner proposes we construe. Thus, we determine that no claim term requires construction for purposes of this decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy").

D. Redundancy of the Asserted Grounds of Unpatentability

Patent Owner argues that we should deny Grounds 4–6 because they are redundant to Grounds 1–3, and Petitioner has made no meaningful distinction between the sets of grounds. Prelim. Resp. 14–15. We decline to exercise our discretion to deny Grounds 4–6 based on Patent Owner's argument. Instead, we address each ground on the merits.

E. Pleading Requirements

Patent Owner argues that we should deny Grounds 2–4 because Petitioner fails to identify with particularity the evidence Petitioner relies upon in those grounds. Prelim. Resp. 49–50. More specifically, Patent Owner argues that the Petition fails:

> "(1) to identify clearly the grounds and references on which Petitioner is relying to assert that the challenged claims are not patentable; (2) to specify where the limitations of the challenged claims are taught or suggested by the cited references; and (3) to provide a sufficiently detailed explanation of the significance of the citations. . . ."

Id. at 48 (quoting *Whole Space Indus. Ltd. v. Zipshade Indus. (B.V.I.) Corp.*, Case IPR2015-00048, slip op. 18 (Paper 14) (PTAB July 24, 2015) and citing 35 U.S.C. § 312(a)(3); 37 C.F.R. §§ 42.22(a)(2), 42.104(b)(2), 42.104(b)(4), 42.104(b)(5)).

With respect to Ground 2, Patent Owner argues that "Petitioner switches between [Lantus Label] and Owens" in presenting its arguments. *Id.* at 49 (citing Pet. 41–43). For Ground 3, Patent Owner argues that Petitioner "obfuscates the nature of its challenge . . . by initially styling that ground as alleging that claims 7 and 24 are obvious over a combination of [Lantus Label] and Grau," but then citing to FASS in the concluding sentence of the argument. *Id.* at 50 (citing Pet. 43). And for Ground 4, Patent Owner argues that although presented as based on the combination of Owens and Lougheed, Petitioner "injects [Lantus Label]" into the ground "as the basis for adding polysorbate 20 and polysorbate 80 to the Owens formulation." *Id.* (citing Pet. 46).

With respect to Grounds 2 and 3, we find that the Petition sets forth (1) each of the references upon which Petitioner relies, (2) where each reference discloses each limitation of the challenged claims (i.e., claims 7 and 24), and (3) why a person of ordinary skill in the art would have been prompted to combine the

teachings of the references, with a reasonable expectation of success in arriving at the claimed invention. *See* Pet. 41–42 (Lantus Label and FASS), 43–45 (Lantus Label and Grau). Rather than an attempt to obfuscate the nature of its challenges, it appears to us that Petitioner's reference to Owens in the concluding sentences of Ground 2 and to FASS in the concluding sentence of Ground 3 are typographical errors. Thus, we treat them as such and do not deny those grounds on that basis.

Regarding Ground 4, it appears that Petitioner's cite to Lantus Label is not a typographical error, or an attempt to include the Lantus Label in the ground. Rather, we consider Petitioner's reference to the Lantus Label as demonstrating common knowledge in the art that would have prompted an ordinary artisan to modify Owens' insulin glargine formulation. *See* Pet. 46; *see also Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006) (rationale for modifying the prior art "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself"). Thus, we do not agree with Patent Owner's assertion that it "is unclear whether Ground 4 is the combination of Owens and Lougheed, or the combination of Owens, Lougheed, and [Lantus Label]." Prelim. Resp. 50. Accordingly, we do not deny Grounds 2–4 for failing to meet the pleading requirements.

F. Asserted References

Before turning to Petitioner's asserted grounds, we provide a brief summary of the asserted references.[10] First, however, we address a preliminary argument

[10] Although we refer to the original pagination associated with each reference in footnotes 1–5, setting forth the full citation of the references, we refer in our discussion to the pagination Petitioner added to each reference.

Patent Owner raises with respect to whether Lantus Label is prior art to the '652 patent.

1. Whether Lantus Label is Prior Art

Patent Owner argues in the Preliminary Response that Petitioner fails to present evidence that Lantus Label is prior art to the '652 patent because the Declaration of Ms. Van Skaik (Ex. 1004A), which Petitioner provides to support the public accessibility of Lantus Label, refers to a version of Exhibit 1004 that is not of record in either proceeding, and the version of Exhibit 1004 that is part of the record does not bear sufficient indicia of public availability. Prelim. Resp. 41–42. With our authorization, Petitioner filed a corrected version of Exhibit 1004 that appears to be the version of the exhibit referenced in Ms. Van Skaik's Declaration. *See* Paper 9, 3–4; corrected Ex. 1004; Ex. 1004A ¶ 5. Petitioner also submitted a Declaration from its counsel (Paper 11) explaining that the version of Exhibit 1004 accompanying the Petition in each proceeding was a working version of the document that counsel inadvertently filed as Exhibit 1004. Thus, Patent Owner's argument appears to be moot.

In any event, Ms. Van Skaik, Executive Director of the Lloyd Library and Museum, testifies that the Lloyd Library and Museum received the Physician's Desk Reference ("PDR") publication containing Lantus Label on December 1, 2000—the same date stamped on the cover page of corrected Exhibit 1004. Ex. 1004A ¶ 5. Ms. Van Skaik further testifies that the PDR publication containing Lantus Label would have been available to the public on December 1, 2000, or shortly thereafter. *Id.* On this record, we find Petitioner shows sufficiently that Lantus Label has been "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence[] can locate it." *Kyocera Wireless Corp. v.*

ITC, 545 F.3d 1340, 1350 (Fed. Cir. 2008). Thus, for purposes of this decision, Petitioner provides adequate evidence to make a threshold showing of public availability such that Lantus Label qualifies as a "printed publication" within the meaning of 35 U.S.C. § 314(a).

2. Lantus Label (Ex. 1004)

Lantus Label describes the commercially available Lantus formulation, a solution of insulin glargine (21^{A}-Gly-30^{B}-a-L-Arg-30^{B}-b-L-Arg-human insulin) for injection that "consists of insulin glargine dissolved in a clear aqueous fluid." Ex. 1004, 3. Each milliliter of Lantus contains 100 IU insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection. *Id.* The pH of Lantus is approximately 4, and is adjusted by adding aqueous solutions of hydrochloric acid and sodium hydroxide to the formulation. *Id.*

Lantus Label also describes the pharmacodynamics of Lantus, explaining that Lantus is "completely soluble" at pH 4, but "[a]fter injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released." *Id.* As a result, Lantus has a relatively constant concentration/time profile, which allows once-daily dosing. *Id.*

Lantus Label instructs that Lantus "must only be used if the solution is clear and colorless with no particles visible." *Id.* at 5; *see also id.* at 6 ("You should look at the medicine in the vial. If the medicine is cloudy or has particles in it, throw the vial away and get a new one.").

3. Owens (Ex. 1005)

Owens describes clinical studies designed to determine the subcutaneous absorption rates of insulin glargine with 15, 30, and 80 µg/ml zinc. Ex. 1005, 1. Owens teaches that insulin glargine is "a di-arginine (30^{B}a-L-Arg-30^{B}b-L-Arg)

human insulin analog in which asparagine at position 21^{A} is replaced by glycine." *Id.* Owens discloses that such a replacement "achieves an increase in the isoelectric point from pH 5.4 (native insulin) to 7.0 and stabilization of the molecule. When injected as a clear acidic solution (pH 4.0), insulin glargine undergoes microprecipitation in the subcutaneous tissue, which retards absorption." *Id.*

In one of the studies, Owens administers subcutaneously a formulation containing 100 IU/ml insulin glargine[15] or insulin glargine[80], m-cresol, and glycerol at pH 4.0, with 15 and 80 µg/ml zinc, respectively. *Id.* at 3. In another study, Owens administers subcutaneously a formulation containing 100 IU/ml insulin glargine, 30 µg/ml zinc, m-cresol, and glycerol at pH 4.0. *Id.* at 4.

4. Lougheed (Ex. 1006)

Lougheed explains that "the tendency of insulin to aggregate during storage in and delivery from [infusion] devices remains one of the fundamental obstacles to their prolonged clinical use." Ex. 1006, 1. In an attempt to address that obstacle, Lougheed describes studies carried out to determine "the effects of physiologic and nonphysiologic compounds on the aggregation behavior of crystalline zinc insulin (CZI) solutions." *Id.* In those studies, Lougheed tested anionic, cationic, and nonionic surfactants, "in view of their known protein-solvation characteristics and their potential to constrain the conformation of insulin[ ] . . . in aqueous solution[,]" to determine whether such surfactants stabilized CZI solutions against aggregation. *Id.* at 1–2. Specifically, Lougheed subjected CZI solutions that contained the surfactants to continuous rotation or shaking to determine whether the surfactants enhanced stability of the CZI solutions as compared to a control of insulin in distilled water. *Id.* at 3. Lougheed

describes the formulation stabilities (FS) of the solutions in terms of continuous rotation (FSR) or shaking (FSS). *Id.*

Lougheed reports that Tween 20, Tween 80, and other "nonionic and ionic surfactants containing the hydrophobic group, $CH_3(CH_2)_N$, with N = 7–16, remarkably stabilized CZI formulations while those lacking such groups demonstrated little or no effect." *Id.* at 1. In Table 3, Lougheed shows the stabilities of formulations containing Tween 20, Tween 80, and other nonionic surfactants. *Id.* at 3–4. Table 3 demonstrates that Tween 20 had an FSR value of 68 days, while Tween 80 had an FSR value of 48 days, as compared to 10 days for the insulin control solutions. *Id.* at 3. Lougheed concludes from the stability data that the nonionic surfactants inhibited aggregate formation in the CZI solution. *Id.*; *see also id.* at 7 (explaining that the nonionic surfactants "markedly increased the stability of their respective formulations when these were subjected to continuous rotation at 37°C").

5. FASS (Ex. 1007A)

FASS describes Insuman Infusat insulin, which is administered as a subcutaneous, intravenous, or intraperitoneal infusion with an insulin pump for the treatment of diabetes mellitus. Ex. 1007A, 5. Each milliliter of the injectable solution contains 100 IU of biosynthetic insulin, 0.058 mg zinc chloride, 6 mg trometamol, 20 mg glycerol, 0.01 mg poly(oxyethylene, oxypropylene)glycol, 2.7 mg phenol (a preservative), 3.7 mg hydrochloric acid, and up to 1 ml water. *Id.* FASS discloses that poly(oxyethylene, oxypropylene)glycol is a stabilizer in the formulation that "prevents precipitation and flocculation of the insulin." *Id.* at 7.

6. Grau (Ex. 1008)

Grau explains that insulin stability "has been a significant impediment in the development of mechanical medication-delivery devices for diabetes," pointing to

the tendency of insulin to "precipitate, aggregate in high-molecular-weight forms, and denature." Ex. 1008, 1. Searching for an insulin preparation to overcome that obstacle, Grau studies the ability of Genapol, a polyethylene-polypropylene glycol, to inhibit insulin aggregation in pump catheters. *Id.*

For the study, Grau uses a "pH-neutral buffered insulin formulation containing either 100 or 400 IU/ml semi-synthetic human insulin [], 27.8 or 111 µg/ml zinc ions (for U-100 and U-400 insulin, respectively) with 2 mg/ml phenol as a preservative, 16 mg/ml glycerol as an isotonicity agent, 50 mM of tris-(hydroxymethyl)-aminomethane (Tris) buffer, and 10 µg/ml polyethylene-polypropylene glycol (Genapol, Hoechst AG, Frankfurt, FRG)." *Id.* Grau tests the insulin formulations in two ways: (1) on a shaking apparatus in a programmable implantable medication system ("PIMS"); and (2) *in vivo* in dogs implanted with the PIMS devices. *Id.* at 2–3. The PIMS devices include a fluid handling system through which the insulin travels, making contact with titanium metal surfaces and the catheter tubing. *Id.* at 2.

Grau analyzes the insulin using scanning electron microscopy and x-ray microanalysis (for the PIMS mounted on the shaking apparatus) or high performance liquid chromatography (for implanted PIMS). *Id.* at 3. Grau reports that changes to the formulations containing Genapol were "comparable to those seen in insulin stored in a glass vial at 37°C without movement," and that the surfaces of the PIMS devices "were clean of apparent precipitate even in remote corners." *Id.* at 4–5. Grau concludes that "Genapol, a surface-active polyethylene-polypropylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces . . . . The data demonstrate good stability in accelerated laboratory tests and after as long as 5 mo between refills in vivo." *Id.* at 6.

G. Ground 1: Asserted Obviousness over the Combination of Lantus Label and Lougheed

Petitioner asserts that claims 1–25 of the '652 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of Lantus Label and Lougheed. Pet. 25–41. Patent Owner opposes. Prelim. Resp. 15–41. Having considered the arguments and evidence before us, for the reasons set forth below, we find that the record establishes a reasonable likelihood that Petitioner will prevail on its asserted ground.

1. Limitations of the Challenged Claims

Petitioner asserts that Lantus Label teaches every limitation of independent claims 1, 7, and 24, except that Lantus Label does not teach "at least one chemical entity chosen from polysorbate 20 and polysorbate 80," as recited in claim 1, or "at least one chemical entity chosen from polysorbate and poloxamers," as recited in claims 7 and 24. *Id.* at 25–26, 29–30 (citing Ex. 1001, 4:27–28; Ex. 1003 ¶¶ 98–102, 129, 160–162, 175–180; Ex. 1004, 3). For those limitations, Petitioner points to Lougheed's teaching of adding polysorbate 20 (Tween 20) or polysorbate 80 (Tween 80) to insulin formulations. *Id.* at 26, 30 (citing Ex. 1003 ¶¶ 163–169, 175–180; Ex. 1006, 4, 7, Table 3). Petitioner makes similar assertions regarding the limitations of the dependent claims, relying on the disclosure of either Lantus Label or Lougheed for teaching the additional limitations of those claims. *See id.* at 31–33, 37–39 (relying on Lougheed for teaching the additional limitations of claims 2, 8, 13, 14, 17–19, 21, and 22); *id.* at 33–36, 39–41 (relying on Lantus Label for teaching the additional limitations of claims 3–6, 9–12, 15, 16, 20, 23, and 25).

At this stage of the proceeding, Patent Owner does not contest Petitioner's arguments or evidence that Lantus Label and Lougheed teach or suggest each limitation of claims 1–25. *See generally* Prelim. Response. On the current record, we find Petitioner shows sufficiently that Lantus Label and Lougheed disclose each limitation of those claims.

The nub of the parties' dispute centers on whether Petitioner shows sufficiently that one of ordinary skill in the art would have had a reason to modify insulin glargine formulations to include Lougheed's disclosed nonionic surfactants, e.g., polysorbate 20 and/or polysorbate 80, and whether the ordinary artisan would have reasonably expected success in achieving the claimed pharmaceutical formulations. We address those issues below.

2. Reason to Modify Lantus Label's Insulin Glargine Formulation

With respect to a reason to modify Lantus Label's insulin glargine formulation, Petitioner asserts it was well-known in the art that insulin had a tendency to aggregate upon storage and delivery. Pet. 26–28 (citing Ex. 1001, 3:2–6; Ex. 1003 ¶¶ 163–169; Ex. 1006, 1). As support, Petitioner points to, *inter alia*, Lougheed's teaching that "the tendency of insulin to aggregate during storage in and delivery from . . . devices remains one of the fundamental obstacles to their prolonged clinical use." Ex. 1006, 1; *see* Pet. 26. Petitioner also directs us to portions of Dr. Yalkowsky's Declaration and the studies he discusses therein. *See id.* at 6–7 (citing Ex. 1003 ¶¶ 105–123, 126). Dr. Yalkowsky testifies that insulin glargine would have been expected to aggregate due to the presence of monomers and its acidic pH environment. Ex. 1003 ¶¶ 105–108, 126 (citing Ex. 1014, 9; Ex. 1015, 3–4, 6; Ex. 1018, 1, 8 Ex. 1031, 1). Additionally, Petitioner asserts that Lantus Label explicitly warns patients not to use the product if aggregation occurs

(i.e., Lantus Label also provides a reason to modify the insulin glargine formulation). Pet. 27 (citing Ex. 1004, 5–6).

Patent Owner responds that Petitioner fails to provide: (1) a prior art disclosure of a glargine aggregation problem; and (2) evidence that a person of ordinary skill in the art would have expected the same aggregation problem for glargine, as was known for human or animal insulin formulations. Prelim. Resp. 16–26. Specifically, Patent Owner argues that Lantus Label describes its solution as "*completely soluble*," and that neither Petitioner nor Dr. Yalkowsky explains why a person of ordinary skill in the art would have understood the "use-only-when-clear" patient instructions in Lantus Label as conveying an aggregation problem. *Id.* at 17 (citing 1004, 3); *see also id.* (explaining that Owens states glargine is a "*clear* acidic solution" with "*stabilization* of the [Glargine] molecule"). Patent Owner also directs us to a number of other parenteral drug products in the PDR that carry the same instruction. *Id.* at 17–18, n.3.

As to insulin glargine and human or animal insulin, Patent Owner contends that Petitioner "conflates Glargine and non-Glargine insulin," even though Petitioner admits that glargine and human insulin are different molecules with different structures, chemical properties, and biological properties. *Id.* at 20–21; *see id.* at 25–26 (citing Ex. 1014, 10, 28). According to Patent Owner, Petitioner's failure to address the differences between glargine and non-glargine insulins renders Petitioner's arguments regarding insulin glargine aggregation "nothing more than . . . conclusory." *Id.* at 22–24.

Patent Owner's argument regarding Lantus Label's patient warning has merit, but Petitioner provides us with additional evidence to support its argument that insulin glargine would have been expected to aggregate. As explained above, Petitioner relies on Lougheed's disclosure that aggregation was a known obstacle

to insulin formulations. *See* Ex. 1006, 1 ("Unfortunately, the tendency of insulin to aggregate during storage in and delivery from . . . devices remains one of the fundamental obstacles to their prolonged clinical use."). Petitioner also cites to the background of the '652 patent, which discusses properties of insulins generally, including insulin glargine and human or animal insulin, without distinguishing between different types of insulin. Ex. 1001, 3:2–6 ("Especially at acidic pH, *insulins* . . . show a decreased stability and an increased proneness to aggregation on thermal and physicomechanical stress, which can make itself felt in the form of turbidity and precipitation (particle formation)." (emphasis added)). Further, Petitioner relies on Dr. Yalkowsky's testimony regarding factors that contribute to insulin aggregation, including acidic pH. Pet. 6–7 (citing Ex. 1003 ¶¶ 103–108, 126). Dr. Yalkowsky's testimony in that regard appears to be supported by objective evidence. *See* Ex. 1003 ¶¶ 103–108 (citing studies of insulin reported in Ex. 1014, 8–9; Ex. 1015, 3–4, 6–7; Ex. 1018, 1, 8; Ex. 1031, 1). At this stage of the proceeding, and based on the current record, we find that Petitioner establishes sufficiently that a person of ordinary skill in the art would have expected insulin glargine to aggregate and, therefore, would have had a reason to modify Lantus Label's insulin glargine formulation.

3. Adding nonionic excipients, such as polysorbate 20 and polysorbate 80, to an insulin glargine formulation

Petitioner asserts that a person of ordinary skill in the art would have modified Lantus Label's formulation by adding nonionic surfactants, such as polysorbate 20 and/or polysorbate 80, because Lougheed expressly discloses that such surfactants enhance the stability of insulin formulations and decrease insulin aggregation. Pet. 26. In that regard, Petitioner directs us to Lougheed's experiments with insulin formulations that include different nonionic surfactants,

e.g., polysorbate 20 and polysorbate 80, in extreme storage conditions. *Id.* (citing Ex. 1006, 1). According to Petitioner, Lougheed's results show that using polysorbate 20 and polysorbate 80 as excipients in insulin formulations enhances stability and decreases aggregate formation. *Id.* (citing Ex. 1003 ¶¶ 163–169; Ex. 1006, 4, 7, Table 3).

Petitioner further asserts that Lougheed's choice of polysorbate 20 and polysorbate 80 as excipients is "not surprising" because polysorbates "were commonly used to stabilize other protein and peptide formulations well prior to June 2002[,]" and already were included in the Food and Drug Administration Inactive Ingredients Guide for various pharmaceutical formulations. *Id.* at 26–27 (citing Ex. 1003 ¶¶ 163–169, 172; Ex. 1016, 3, Table I). Thus, argues Petitioner, a person of ordinary skill in the art "would have had ample reason" to add polysorbate 20 and/or polysorbate 80 to an insulin glargine formulation, "with a reasonable expectation that doing so would successfully inhibit or eliminate insulin's well-known propensity to aggregate." *Id.* at 27.

In response, Patent Owner first argues that Petitioner fails to show sufficiently that the ordinary artisan would have turned to Lougheed (or any other non-glargine asserted reference). Prelim. Resp. 27. Specifically, Patent Owner asserts that Petitioner fails to address the differences between the glargine formulation Lantus Label describes and the porcine insulin formulations that Lougheed describes. *Id.* at 28. Patent Owner explains that, in addition to protein type, those differences include formulation pH (acidic for Lantus Label vs. neutral/basic for Lougheed and Grau or none specified for FASS) and formulation delivery type (injection for Lantus Label vs. pump for Lougheed, FASS, and Grau). *Id.* Patent Owner contends that such differences matter, and that Petitioner's failure to address them is a "significant deficiency." *Id.* at 29.

With respect to protein type, Patent Owner asserts the prior art of record indicates that "differences in the amino acid chains of human and animal insulins can result in large differences in aggregation tendencies, in unpredictable ways." *Id.* (citing Ex. 1014, 2; Ex. 1015, 2). As explained above, however, the '652 patent specification refers to what was known about insulins generally, without distinguishing between glargine (i.e., modified insulin), human, and animal insulin. *See* Ex. 1001, 3:2–4 ("Especially at acidic pH, insulins . . . show a decreased stability and an increased proneness to aggregation"), 3:32–34 ("The present invention was thus based on the object of finding preparations for acid-soluble insulins containing surfactants"), 3:41–43 ("It has now surprisingly been found that the addition of surfactants can greatly increase the stability of acidic insulin preparations. . . ."); *see also* Ex. 1001A, 2817 (original claim 1 of the application that matured into the '652 patent reciting a pharmaceutical formulation with an acidic pH comprising "a polypeptide selected from the group consisting of bovine, porcine, or human insulin, an insulin analogue, an insulin derivative, an active insulin metabolite and combinations thereof").

As to pH, Patent Owner contends that none of the cited references addresses stabilizing a protein in an acidic solution, and that Petitioner fails to explain why a person of ordinary skill in the art would have been prompted to combine glargine formulations at acidic pH with Lougheed's animal insulin formulations at neutral/basic pH. *Id.* at 29–30. Petitioner, however, does not argue that one of ordinary skill in the art would have modified Lantus Label's insulin glargine formulation with neutral/basic pH non-glargine insulin formulations.

Rather, Petitioner argues that the ordinary artisan would have been prompted to modify the insulin glargine formulation to include polysorbate 20 and/or polysorbate 80 as excipients, given the prior art teachings that such excipients were

known to stabilize insulin formulations against aggregation and that acidic pH was known to contribute to aggregation. *See* Pet. 6–7 (citing Ex. 1003 ¶¶ 103–108, 126), 27–28; Ex. 1006, 3 (explaining that observed FSR values for insulin formulations including Tween 20 (i.e., polysorbate 20) and Tween 80 (i.e., polysorbate 80) are 68 days and 48 days, respectively, as compared with 10 days for insulin controls (i.e., formulations that lacked surfactant additives), 7 ("With respect to the stabilizers employed, it is apparent that all the anionic and nonionic detergent additives [i.e., surfactants], with the exception of Tween 60, markedly increased the stability of their respective formulations when these were subjected to continuous rotation at 37°C."), Table 3. Further, in making its argument, Patent Owner does not direct us to any evidence in the record suggesting that the pH of the formulation would have had an effect on the ability of polysorbate 20 and polysorbate 80 to stabilize an insulin glargine formulation.

Regarding route of administration, Patent Owner argues that Petitioner fails to explain why a person of ordinary skill in the art "would have looked to formulations tested under the mechanical stresses and materials used in insulin pumps for continuous infusion, and have combined these components with those from the once-daily subcutaneous injection Glargine." Prelim. Resp. 31. In making its argument, however, Patent Owner does not direct us to evidence in the record suggesting why differences between pump materials and injectable materials would have mattered to the ordinary artisan. To the contrary, the '652 patent and prior art appear to suggest that air-insulin interfaces and interactions with hydrophobic surfaces promote insulin aggregation, not the type of material used to deliver the insulin formulation. *See, e.g.*, Ex. 1001, 3:8–17; Ex. 1006, 2.

4. Teaching Away and Other Negative Consequences

Patent Owner also argues that Petitioner fails to account for disclosures in the prior art that support nonobviousness. Specifically, Patent Owner argues that Lougheed teaches away from selecting a nonionic surfactant (Prelim. Resp. 35–38), and that Petitioner fails to account for the disclosure of negative consequences in other prior art of record (*id.* at 38–40). With respect to teaching away, Petitioner argues that Lougheed would have directed a person of ordinary skill in the art to use anionic surfactants, specifically sodium dodecyl sulfate (SDS), and away from nonionic surfactants, such as polysorbate 20 and polysorbate 80. *Id.* at 35. This is so, argues Patent Owner, because (1) Lougheed reports achieving better stability results with SDS than with the polysorbate additives, and (2) Lougheed hypothesizes that anionic surfactants stabilize the monomeric form of insulin (i.e., the form of insulin Petitioner argues is prevalent in insulin glargine), whereas nonionic surfactants stabilize dimers and higher order structures. *Id.* at 35–38.

At this stage of the proceeding, we are not persuaded that Lougheed teaches away from adding polysorbate 20 and/or polysorbate 80 to Lantus Label's insulin glargine formulation. Even assuming that Lougheed discloses a preference for using SDS as an excipient, that preference does not control the obviousness inquiry. Rather, we must consider all disclosures, even unpreferred embodiments, in an obviousness analysis. *Merck & Co. v. Biocraft Labs, Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). And, as Petitioner explains, Lougheed expressly discloses that adding nonionic surfactants, such as polysorbate 20 and polysorbate 80, to an insulin formulation enhances stability and decreases aggregate formation. Pet. 26 (citing Ex. 1006, 4, 7, Table 3); Ex. 1006, 7 ("all the anionic and nonionic detergent additives, with the exception of Tween 60, markedly increased the stability of their respective formulations when the[y] were subjected to continuous

rotation at 37°C."); *see id.* at 3 ("As is evident from the FS values, aggregate formulation was inhibited by the nonionics . . . Tween 20 . . . [and] Tween 80. . . . FSR values for these solutions were respectively . . . 68 [and] 48 . . . as compared with 10 days for the insulin controls.").

Further, we find that Patent Owner's argument regarding Lougheed's "hypothesis" that nonionic surfactants stabilize dimer or higher polymers raises a factual dispute as to whether one of skill in the art would have been discouraged from including polysorbate 20 and/or polysorbate 80 as excipients in an insulin glargine formulation. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). That dispute is best resolved on the full trial record, and we invite the parties to address the issue further in the Response and Reply.

With respect to the negative consequences of certain formulation excipients, Patent Owner directs us to portions of the 1994 Handbook of Pharmaceutical Excipients ("Handbook")[11] teaching that polysorbates were known to undergo hydrolysis in an acidic environment, and that using polysorbates in a formulation that contains phenol can result in discoloration and/or precipitation. Prelim. Resp. 39–40. Patent Owner also directs us to the Handbook entry for cresol, which states that its "[a]ntimicrobial activity is reduced in the presence of nonionic surfactants." Ex. 1019, 5; Prelim. Resp. 40.

Patent Owner's arguments are not without merit. We find, however, that they raise factual disputes as to whether one of skill in the art would have been discouraged from including polysorbate 20 and/or polysorbate 80 as excipients in

[11] HANDBOOK OF PHARMACEUTICAL EXCIPIENTS 139, 377 (Ainley Wade & Paul J. Weller eds., 2d ed. 1994) (Ex. 1019). Although we refer to the original pagination in this citation, like Patent Owner, we refer in our discussion to the pagination Petitioner added to the exhibit.

the Lantus Label insulin glargine formulation, which is acidic and includes m-cresol as an excipient. For example, although Patent Owner points to the Handbook's disclosure that "gradual saponification [of polysorbates] occurs with strong acids," it is not clear from the current record what the person of ordinary skill in the art would have understood from such teaching. Nor is it apparent from the current record that one of ordinary skill in the art would have been discouraged from using polysorbates as excipients with phenol or cresol in light of the Handbook's teachings regarding discoloration and antimicrobial activity. As our reviewing court has explained, "a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). We invite the parties to address these issues further in the Response and Reply.

In sum, on the present record, we find that Petitioner establishes a reasonable likelihood of prevailing in showing that a person of ordinary skill in the art would have been prompted to add polysorbate 20 and/or polysorbate 80 as excipients to an insulin glargine formulation, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations.

H. Grounds 2 and 3: Asserted Obviousness over the Combination of Lantus Label and FASS or Lantus Label and Grau

Petitioner asserts that claims 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of Lantus Label and FASS or Grau. Pet. 41–45. Patent Owner opposes. Prelim. Resp. 15–41. Having considered the arguments and evidence before us, for the reasons set forth below, we find that the record establishes a reasonable likelihood that Petitioner will prevail on its asserted grounds.

Petitioner's arguments are substantially the same as those for claims 7 and 24 in Ground 1, except that Petitioner cites FASS or Grau instead of Lougheed. Petitioner argues that Lantus Label teaches all of the elements of claims 7 and 24, except that Lantus Label does not teach "at least one chemical entity chosen from polysorbate and poloxamers," as recited in both claims. Pet. 41–42 (Lantus Label and FASS), 43 (Lantus Label and Grau). For that limitation in Ground 2, Petitioner directs us to FASS' teaching that adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer) to an insulin formulation "prevents precipitation and flocculation of the insulin," which makes the formulation "particularly suited for use in insulin pumps." *Id.* at 42 (quoting Ex. 1007A, 7); *see id.* (citing Ex. 1033A, 6). For that limitation in Ground 3, Petitioner directs us to Grau's teaching of adding a poloxamer (Genapol) to insulin formulations "to inhibit insulin aggregation" for various *in vitro* and *in vivo* tests with PIMS devices. *Id.* at 43–44 (citing Ex. 1008, 2–6).

As with Ground 1, Petitioner argues that a person of ordinary skill in the art would have been prompted to modify Lantus Label's insulin glargine formulation to include poloxamers, such as those disclosed in FASS and Grau, in view of the well-known tendency for insulin to aggregate upon storage and delivery—a recognized obstacle to formulating insulins. *Id.* at 42, 44–45. And, like Ground 1, Petitioner supports its assertions with citations to the prior art, as well as Dr. Yalkowsky's testimony. *Id.* (citing Ex. 1006, 1; Ex. 1003 ¶¶ 223–229, 231–237); *see* Ex. 1008, 1 (describing insulin's tendency to precipitate and aggregate). Likewise, Petitioner argues that a person of ordinary skill in the art would have reasonably expected success in achieving the claimed pharmaceutical formulations. Pet. 42, 44–45.

Patent Owner does not provide separate arguments for Grounds 2 and 3 to address Petitioner's assertions that a person of ordinary skill in the art would have been prompted to modify Lantus Label's insulin glargine formulation to include poloxamers as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations. Rather, Patent Owner's arguments in that regard address Grounds 1–6 collectively. *See, e.g.*, Prelim. Resp. 15 (addressing all six of Petitioner's asserted grounds together), 27 (same), 33 (same).

As explained above with respect to Ground 1, we find that Patent Owner's arguments raise disputed issues of material fact that are best resolved on a full trial record. *See supra* §§ III.G.2–III.G.4. Accordingly, for substantially the same reasons set forth above, we find that Petitioner demonstrates a reasonable likelihood that the combined teachings of Lantus Label and FASS (Ground 2) or Lantus Label and Grau (Ground 3) disclose each limitation of claims 7 and 24, and that one of ordinary skill in the art would have modified Lantus Label's insulin glargine formulation to include poloxamers as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations.

I. Ground 4: Asserted Obviousness over the Combination of Owens and Lougheed

Petitioner asserts that claims 1–25 of the '652 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of Owens and Lougheed. Pet. 25–41. Patent Owner opposes. Prelim. Resp. 15–41. Having considered the arguments and evidence before us, for the reasons set forth below, we find that the record establishes a reasonable likelihood that Petitioner will prevail on its asserted ground.

Petitioner's arguments are substantially the same as those for Ground 1, except that Petitioner cites Owens instead of Lantus Label. As with Lantus Label,

Petitioner argues that Owens teaches all of the elements of independent claims 1, 7, and 24, except that Owens does not teach "at least one chemical entity chosen from polysorbate 20 and polysorbate 80," as recited in claim 1, or "at least one chemical entity chosen from polysorbate and poloxamers," as recited in claims 7 and 24. Pet. 45–48 (citing Ex. 1001, 4:27–28; Ex. 1003 ¶¶ 98–102, 239; Ex. 1005, 3–4). For those limitations, Petitioner points to Lougheed's teaching of adding polysorbate 20 (Tween 20) or polysorbate 80 (Tween 80) to insulin formulations. *Id.* at 26, 30 (citing Ex. 1003 ¶¶ 126, 239–246, 249–253; Ex. 1006, 427, 430, Table 3). Petitioner makes similar assertions regarding the limitations of the dependent claims, relying on the disclosure of either Owens or Lougheed for teaching the additional limitations of those claims. *See id.* at 48–50, 52–54, 55–56 (relying on Lougheed for teaching the additional limitations of claims 2, 8, 13, 14, 17–19, 21, 22, and 25); *id.* at 50–52, 54–55 (relying on Owens for teaching the additional limitations of claims 3–6, 9–12, 15, 16, 20, and 23).

As with Ground 1, Petitioner argues that a person of ordinary skill in the art would have been prompted to modify Owens' insulin glargine formulation to include polysorbate 20 and polysorbate 80, in view of the well-known tendency for insulin to aggregate upon storage and delivery. Pet. 45–48. And, like Ground 1, Petitioner supports its assertions with citations to Lougheed and Dr. Yalkowsky's testimony. *Id.* (citing Ex. 1003 ¶¶ 126, 239–246, 249–253; Ex. 1006, 4, 7, Table 3). Likewise, Petitioner argues that a person of ordinary skill in the art would have reasonably expected success in achieving the claimed pharmaceutical formulations. *Id.*

Patent Owner does not provide separate arguments for Ground 4 to address Petitioner's assertions that a person of ordinary skill in the art would have been prompted to modify Owens' insulin glargine formulation to include polysorbate 20

and/or polysorbate 80 as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations. Rather, Patent Owner's arguments in that regard address Grounds 1–6 collectively. *See, e.g.*, Prelim. Resp. 15 (addressing all six of Petitioner's asserted grounds together), 27 (same), 33 (same).

As explained above with respect to Ground 1, we find that Patent Owner's arguments raise disputed issues of material fact that are best resolved on a full trial record. *See supra* §§ III.G.2–III.G.4. Accordingly, for substantially the same reasons set forth above, we find that Petitioner demonstrates a reasonable likelihood that the combined teachings of Owens and Lougheed disclose each limitation of claims 1–25, and that one of ordinary skill in the art would have modified Owens' insulin glargine formulation to include polysorbate 20 and/or polysorbate 80 as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations.

J. Grounds 5 and 6: Asserted Obviousness over the Combination of Owens and FASS or Owens and Grau

Petitioner asserts that claims 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103(a) because the subject matter of those claims would have been obvious over the combination of Owens and FASS or Grau. Pet. 56–60. Patent Owner opposes. Prelim. Resp. 15–41. Having considered the arguments and evidence before us, for the reasons set forth below, we find that the record establishes a reasonable likelihood that Petitioner will prevail on its asserted grounds.

Petitioner's arguments are substantially the same as those for claims 7 and 24 in Grounds 1–4, except that Petitioner cites FASS or Grau instead of Lougheed, and Owens instead of Lantus Label. Petitioner argues that Owens teaches all of the

elements of claims 7 and 24, except that Owens does not teach "at least one chemical entity chosen from polysorbate and poloxamers," as recited in both claims. Pet. 56–57 (Owens and FASS), 58–59 (Owens and Grau). For that limitation in Ground 5, Petitioner directs us to FASS' teaching that adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer) to an insulin formulation "prevents precipitation and flocculation of the insulin," which makes the formulation "particularly suited for use in insulin pumps." *Id.* at 57 (quoting Ex. 1007A, 7); *see id.* (citing Ex. 1033A, 6). For that limitation in Ground 6, Petitioner directs us to Grau's teaching of adding a poloxamer (Genapol) to insulin formulations "to inhibit insulin aggregation" for various *in vitro* and *in vivo* tests with PIMS devices. *Id.* at 58–59 (citing Ex. 1008, 2–6).

As with Grounds 1–4, Petitioner argues that a person of ordinary skill in the art would have been prompted to modify Owens' insulin glargine formulation to include poloxamers, such as those disclosed in FASS and Grau, in view of the well-known tendency for insulin to aggregate upon storage and delivery—a recognized obstacle to insulin formulating. Pet. 57–59. And, like Grounds 1–4, Petitioner supports its assertions with citations to the prior art, as well as Dr. Yalkowsky's testimony. *Id.* (citing Ex. 1006, 1; Ex. 1003 ¶¶ 297–300, 302–306); *see also* Ex. 1008, 1 (describing insulin's tendency to precipitate and aggregate as an impediment to developing delivery devices for treating diabetes). Likewise, Petitioner argues that a person of ordinary skill in the art would have reasonably expected success in achieving the claimed pharmaceutical formulations. Pet. 57–60.

Patent Owner does not provide separate arguments for Grounds 5 and 6 to address Petitioner's assertions that a person of ordinary skill in the art would have been prompted to modify Owens' insulin glargine formulation to include

poloxamers as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations. Rather, Patent Owner's arguments in that regard address Grounds 1–6 collectively. *See, e.g.*, Prelim. Resp. 15 (addressing all six of Petitioner's asserted grounds together), 27 (same), 33 (same).

As explained above with respect to Ground 1, we find that Patent Owner's arguments raise disputed issues of material fact that are best resolved on a full trial record. *See supra* §§ III.G.2–III.G.4. Accordingly, for substantially the same reasons set forth above, we find that Petitioner demonstrates a reasonable likelihood that the combined teachings of Owens and FASS (Ground 5) or Owens and Grau (Ground 6) disclose each limitation of claims 7 and 24, and that one of ordinary skill in the art would have modified Owens' insulin glargine formulation to include poloxamers as excipients, with a reasonable expectation of success in achieving the claimed pharmaceutical formulations.

IV. CONCLUSION

Petitioner establishes a reasonable likelihood of prevailing in challenging claims 1–25 of the '652 patent, and Patent Owner's arguments and evidence in the Preliminary Response do not persuade us otherwise. Although many of Patent Owner's arguments raise genuine issues of material fact, the parties will have the opportunity to further develop these facts during trial, and the Board will evaluate the fully-developed record at the close of the evidence.

Accordingly, taking account of the information presented in the Petition and the Preliminary Response, and the evidence of record, we determine that Petitioner establishes a reasonable likelihood that it will prevail in showing that claims 1–25 of the '652 patent are unpatentable. Our findings and conclusions are not final and may change upon consideration of the full record developed during trial.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is granted and an *inter partes* review is instituted as to:

Claims 1–25 of the ’652 patent under 35 U.S.C. § 103 over the combination of Lantus Label and Lougheed;

Claims 7 and 24 of the ’652 patent under 35 U.S.C. § 103 over the combination of Lantus Label and FASS;

Claims 7 and 24 of the ’652 patent under 35 U.S.C. § 103 over the combination of Lantus Label and Grau;

Claims 1–25 of the ’652 patent under 35 U.S.C. § 103 over the combination of Owens and Lougheed;

Claims 7 and 24 of the ’652 patent under 35 U.S.C. § 103 over the combination of Owens and FASS; and

Claims 7 and 24 of the ’652 patent under 35 U.S.C. § 103 over the combination of Owens and Grau;

FURTHER ORDERED that no other ground of unpatentability is authorized;

FURTHER ORDERED that notice is hereby given of the institution of a trial commencing on the entry date of this decision, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4; and

FURTHER ORDERED that Petitioner shall update its mandatory notices, within three days of the entry of this Decision, to include as related matters the pending and concluded litigation that Patent Owner identifies and IPR2017-01528.

IPR2017-01526
Patent 7,476,652 B2

PETITIONER:
Jeffrey Guise
Douglas Carsten
Richard Torczon
Lorelei Westin
Clark Lin
Nancy Zhang
WILSON SONSINI GOODRICH & ROSATI
jguise@wsgr.com
dcarsten@wsgr.com
rtorczon@wsgr.com
lwestin@wsgr.com
clin@wsgr.com
nzhang@wsgr.com

PATENT OWNER:
Elizabeth Weiswasser
Anish Desai
Aaron Pereira
WEIL, GOTSHAL & MANGES LLP
elizabeth.weiswasser@weil.com
anish.desai@weil.com
aaron.pereira@weil.com

EXHIBIT 5

Trials@uspto.gov
571-272-7822

Paper No. 89
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

SANOFI-AVENTIS DEUTSCHLAND GMBH,
Patent Owner.

Case IPR2017-01526
Patent 7,476,652 B2

Before ERICA A. FRANKLIN, ROBERT A. POLLOCK, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges.*

ANKENBRAND, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

Finding Claims 1–25 Unpatentable
35 U.S.C. § 318(a); 37 C.F.R. § 42.73

Denying-in-part and Dismissing-in-part as Moot Patent Owner's Motion to Strike
37 C.F.R. §§ 42.5(a), 42.20(a)

Dismissing Petitioner's Motion to Exclude and Denying-in-part and Dismissing-in-part as Moot Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Granting Petitioner's First Motion to Seal, Denying Petitioner's Second Motion to Seal, and Granting Patent Owner's Motions to Seal
37 C.F.R. § 42.54

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–25 (collectively, the "challenged claims") of U.S. Patent No. 7,476,652 B2 (Ex. 1001, "the '652 patent"). We have jurisdiction under 35 U.S.C. § 6. For the reasons that follow, we determine that Petitioner demonstrates, by a preponderance of the evidence, that the challenged claims are unpatentable.

A. *Procedural History*

Mylan Pharmaceuticals, Inc. ("Petitioner") filed a Petition (Paper 2, "Pet.") requesting an *inter partes* review under 35 U.S.C. § 311. Petitioner supported its Petition with the testimony of Samuel H. Yalkowsky, Ph.D. (Ex. 1003). On December 13, 2017, we instituted trial to determine whether:

1. Claims 1–25 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Lantus Label[1] and Lougheed[2];
2. Claims 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Lantus Label and FASS[3];

[1] Physicians' Desk Reference, Lantus entry 709–13 (55th ed. 2001) (Ex. 1004). We refer in this decision to the corrected version of Exhibit 1004.

[2] W.D. Lougheed et al., *Physical Stability of Insulin Formulations*, 32 DIABETES 424–32 (1983) (Ex. 1006).

[3] Farmaceutiska Specialiteter I Sverige ("FASS"), Summary of Product Characteristics Entry for Insuman Infusat (2000) (certified English translation provided as Ex. 1007A; original Swedish version provided as Ex. 1007).

3. Claims 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Lantus Label and Grau[4];
4. Claims 1–25 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Owens[5] and Lougheed;
5. Claims 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Owens and FASS; and
6. Claims 7 and 24 of the '652 patent are unpatentable under 35 U.S.C. § 103 as obvious over the combination of Owens and Grau.

Paper 13 ("Institution Decision" or "Inst. Dec.").

Following institution, Sanofi-Aventis Deutschland GmbH ("Patent Owner") filed a Response (Paper 27, "Resp.") and supporting declarations from Bernhardt Trout, Ph.D. (Ex. 2006) and Laurence C. Baker, Ph.D. (Ex. 2039). Petitioner filed a Reply (Paper 43, "Reply") and supporting declarations from Dr. Yalkowsky (Ex. 1181), Robert S. Langer, Sc.D. (Ex. 1111), Deforest McDuff, Ph.D. (Ex. 1169), and William C. Biggs, M.D. (Ex. 1174).

During an interlocutory teleconference on July 17, 2018, we authorized Patent Owner to file a motion to strike certain arguments Petitioner made in the Reply. *See* Ex. 2055, 43:3–20 (Transcript of July 17, 2018 teleconference). We also authorized Patent Owner to file a sur-reply as to certain, but not all, arguments in Petitioner's Reply. *Id.* at 42:13–43:2. Subsequently, Patent Owner filed a Sur-reply (Paper 46) and a Motion to Strike (Paper 47, "Mot. to Strike"). Petitioner

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[4] Ulrich Grau & Christopher D. Saudek, *Stable Insulin Preparation for Implanted Insulin Pumps – Laboratory & Animal Trials*, 36 DIABETES 1453–59 (1987) (Ex. 1008).

[5] David R. Owens et al., *Pharmacokinetics of ^{125}I-Labeled Insulin Glargine (HOE 901) in Healthy Men – Comparison with NPH insulin and the influence of different subcutaneous injection sites*, 23 DIABETES CARE 813–19 (2000) (Ex. 1005).

filed an opposition to Patent Owner's Motion to Strike (Paper 52, "Mot. to Strike Opp.").

Petitioner and Patent Owner also filed several motions to seal certain briefs and exhibits. Paper 41 (Petitioner's Motion to Seal and for Entry of Proposed Protective Order), Paper 45 (Patent Owner's Supplemental Motion to Seal), Paper 78 (Patent Owner's Motion to Seal), Paper 87 (Petitioner's Motion to Seal). Both parties also filed motions to exclude, which have been fully briefed. *See* Papers 57, 64, 79 (briefing related to Petitioner's Motion to Exclude); Papers 61, 67, 71 (briefing related to Patent Owner's Motion to Exclude). Patent Owner also filed Observations on the Cross-Examination Testimony of Petitioner's Reply Declarants, and Petitioner responded. Papers 60, 68. The record further includes a transcript of the final oral hearing conducted on September 27, 2018. Paper 77 ("Tr.").

After the final oral hearing, we authorized Patent Owner to file a second sur-reply and additional evidence, and we authorized Petitioner to file a sur-sur-reply. Paper 75. Subsequently, Patent Owner filed the Sur-reply (Papers 79 (confidential version), 80 (public version)), and Petitioner filed the Sur-sur-reply (Papers 86 (confidential version), 88 (public version)).

B. *Related Matters*

The parties identify the following pending litigation involving the '652 patent: *Sanofi-Aventis U.S. LLC v. Merck Sharp & Dohme Corp.*, C.A. No. 1:16-cv-00812-RGA (D. Del.); *Sanofi-Aventis U.S. LLC v. Merck Sharp & Dohme Corp.*, C.A. No. 2:17-cv-05914 (D.N.J.); *Sanofi- Aventis U.S. LLC v. Mylan N.V.*, C.A. No. 2:17-cv-09105-SRC (D.N.J); and *Sanofi- Aventis U.S. LLC v. Mylan N.V.*, C.A. No. 1:17-cv-00181-IMK (D.W.V.). Paper 7, 2; Paper 14, 1–2. The parties also identify the following concluded litigation involving the '652 patent:

Sanofi-Aventis U.S. LLC v. Eli Lilly & Co., C.A. No. 1:14-cv-00113-RGA (D. Del.); *Sanofi-Aventis U.S. LLC v. Eli Lilly & Co.*, C.A. No. 1:14-cv-00884-RGA (D. Del.). Paper 7, 2; Paper 14, 1.

And the parties identify as related Case IPR2017-01528— an *inter partes* review involving claims 1–20 of U.S. Patent No. 7,713,930 (Ex. 1002), which issued from a continuation application to the application that issued as the '652 patent. Paper 7, 2; Paper 14, 2. Concurrent with this decision, we issue a Final Written Decision in Case IPR2017-01528.

C. *The '652 Patent (Ex. 1001)*

The '652 patent, titled "Acidic Insulin Preparations Having Improved Stability," issued on January 13, 2009. Ex. 1001, (45), (54). The '652 patent relates to pharmaceutical formulations comprising a modified insulin—insulin glargine (Gly(A21)-Arg(B31)-Arg(B32)-human insulin) —and at least one surfactant. *See, e.g.*, Ex. 1001, Abstract, 1:11–19, 11:2–9. The formulation is used to treat diabetes, and is "particularly suitable for preparations in which a high stability to thermal and/or physicomechanical stress is necessary." *Id.* at 1:19–22. According to the specification, insulin glargine was a known modified insulin with a prolonged duration of action injected once daily as an acidic, clear solution that "precipitates on account of its solution properties in the physiological pH range of the subcutaneous tissue as a stable hexamer associate." *Id.* at 2:56–61.

The specification explains that, at acidic pH, insulins exhibit decreased stability and increased susceptibility to aggregation in response to thermal and physicomechanical stress, resulting in turbidity and precipitation (i.e., particle formation). *Id.* at 3:2–6. Such stresses can arise during use or shaking of the insulin solution. *Id.* at 5:34–56. Also contributing to aggregation are hydrophobic surfaces with which the insulin solution comes into contact during storage and

administration, including those on glass storage vessels, solution/air boundary layers, sealing cap stopper materials, and siliconized insulin syringes. *Id.* at 3:8–17.

According to the specification, the applicants "surprisingly [] found" that adding surfactants to the insulin solution or formulation "can greatly increase the stability of acidic insulin preparations," thereby producing insulin solutions with "superior stability to hydrophobic aggregation nuclei for several months [u]nder temperature stress." *Id.* at 3:41–45; *see id.* at 5:20–10:67 (examples showing that adding the surfactant polysorbate 20 or polysorbate 80 to an insulin glargine formulation stabilizes the formulation in use and during physicomechanical stressing).

D. *Illustrative Claim*

We instituted an *inter partes* review of claims 1–25 of the '652 patent, of which claims 1, 7, and 24 are independent. Claim 1 is illustrative of the claimed subject matter and recites:

> 1. A pharmaceutical formulation comprising Gly(A21), Arg(B31), Arg(B32)-human insulin;
>
> at least one chemical entity chosen from polysorbate 20 and polysorbate 80;
>
> at least one preservative; and
>
> water,
>
> wherein the pharmaceutical formulation has a pH in the acidic range from 1 to 6.8.

Ex. 1001, 11:2–9.

II. EVIDENTIARY MOTIONS

Patent Owner filed a motion to strike various arguments and evidence. Petitioner and Patent Owner also filed motions to exclude certain evidence. We

first address Patent Owner's motion to strike and then turn to the parties' motions to exclude.

A. *Patent Owner's Motion to Strike*

Patent Owner requests to strike what it contends are two new arguments that Petitioner makes based on Lantus Label: (1) that Lantus Label's teaching of different storage requirements for different product sizes would have indicated an aggregation problem and provided a reason to modify the Lantus Label formulation; and (2) that Lantus Label sometimes refers to insulin glargine as "insulin," which would have suggested that it "'behaved similar to other insulins.'" Mot. to Strike 1–2. Patent Owner also seeks to strike paragraphs 100 and 120–26 of Dr. Langer's declaration (Ex. 1111), as well as paragraphs 8 and 20–22 of Dr. Yalkowsky's reply declaration (Ex. 1181). *Id.* at 1. According to Patent Owner, the arguments and testimony are outside the scope of a proper reply. Petitioner opposes. Mot. to Strike Opp. 1–2.[6]

We do not rely on the arguments or evidence that Patent Owner seeks to strike in making our ultimate determination on the patentability of the challenged claims. Thus, we dismiss Patent Owner's request as moot.

Patent Owner next argues that we should strike what it contends are new arguments and evidence (Ex. 1111 ¶¶ 147, 159, 161) based on new insulin references. Mot. to Strike 2–3. Specifically, Patent Owner directs us to Petitioner's argument that an ordinarily skilled artisan would have reasonably expected success because "at least 20 prior art references allegedly show

[6] Patent Owner filed a sur-reply addressing Petitioner's argument about the different storage requirements for different Lantus product sizes and additional evidence supporting its sur-reply. Paper 79; Exs. 2060–2069. And Petitioner filed a sur-sur-reply in response to Patent Owner's sur-reply on this issue. Paper 86.

surfactants tried with proteins, and at least 12 references allegedly show surfactants with insulin (not glargine)." *Id.* at 3. Patent Owner contends that this argument and supporting evidence amounts to "a do-over" "with new references presented through a new expert." *Id.* Petitioner opposes, arguing that the Petition provides evidence that the claimed surfactants were commonly used in protein formulations and provides one example for insulin. Mot. to Strike Opp. 2. Petitioner further asserts that the argument and evidence are properly submitted in reply because they directly respond to Patent Owner's argument that an ordinarily skilled artisan would not have reasonably expected success because of "alleged unpredictable effects that surfactants 'could' have or that 'were possible.'" *Id.* at 3 (citing Resp. 49, 52).

We agree with Petitioner that its argument and evidence is within the proper scope of a reply. The argument does not raise a new theory of unpatentability or provide new references in support of Petitioner's prima facie obviousness case. Rather, we find that the formulations discussed in the Reply and Dr. Langer's declaration support the initial arguments raised in the Petition and directly respond to Patent Owner's arguments about reasonable expectation of success and further serve to "document the knowledge that skilled artisans would bring to bear in reading the prior art identified as producing obviousness." *Anacor Pharm., Inc. v. Iancu*, 889 F.3d 1372, 1380–81 (Fed. Cir. 2018); *see Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1365 (Fed. Cir. 2015); *Belden Inc. v. Berk-Tek LLC*, 804 F.3d 1064, 1078–80 (Fed. Cir. 2015) (explaining that the Board may rely on new evidence submitted with a reply because that evidence was responsive to the arguments in patent owner's response). Accordingly, we deny Patent Owner's request to strike Petitioner's argument and Dr. Langer's testimony about additional insulin formulations.

Patent Owner next requests that we strike Petitioner's reply argument and evidence (Ex. 1111 ¶¶ 127–145; Ex. 1133; Ex. 1174) about "'public' knowledge," arguing that Petitioner presents a new theory based on documents about a recall, and hearsay evidence from a new fact witness about a Lantus vial that became turbid in a hot car. Mot. to Strike 4–5. Patent Owner also argues that Petitioner improperly relies on Patent Owner's confidential internal documents to support the obviousness challenge. *Id.* According to Patent Owner, Petitioner's argument is not responsive to anything in the Response. *Id.* at 5. Petitioner opposes, arguing that it has not presented any new theory. Mot. to Strike Opp. 4–5.

We do not rely on the arguments or evidence that Patent Owner seeks to strike in making our ultimate determination on the patentability of the challenged claims. Thus, we dismiss Patent Owner's request as moot.

Finally, Patent Owner requests that we strike the Reply and Dr. Langer's declaration in their entirety. Mot. to Strike 5–7. Patent Owner argues that "Petitioner is attempting a complete re-do of its Petition, contrary to the letter and spirit of the IPR framework." *Id.* at 6. Patent Owner further argues that Dr. Langer's declaration is "an 87-page declaration from a new expert who . . . offers alleged support for a number of new theories and presents almost 60 new exhibits." *Id.* at 5. Petitioner opposes, arguing that both its Reply and Dr. Langer's declaration are proper. Mot. to Strike Opp. 5–7.

We do not agree with Patent Owner that Petitioner's Reply and Dr. Langer's declaration are improper. Rather, we find that the Reply and Dr. Langer's declaration support the initial arguments raised in the Petition, are in fair response to the arguments Patent Owner raises in the Response, and also fairly respond to Dr. Trout's testimony. *Belden Inc.*, 804 F.3d at 1078. Further, Patent Owner has been granted, and indeed, filed two sur-replies addressing arguments made in

Petitioner's Reply and Petitioner's supporting evidence. Papers 46, 79. Accordingly, we deny Petitioner's request to strike the Reply and Dr. Langer's declaration in their entirety.

In sum, we deny-in-part and dismiss-in-part as moot Patent Owner's Motion to Strike.

B. *Motions to Exclude*

Petitioner and Patent Owner each filed a motion to exclude. We address Petitioner's motion first and then turn to Patent Owner's motion.

1. Petitioner's Motion to Exclude

Petitioner moves to exclude Exhibits 2042–2045 and Exhibits 2051–2052. Paper 57 ("Pet. Mot. to Exclude"). Exhibits 2042–2045 are certain documents Dr. Baker relied upon to support his opinions regarding the commercial success of the Lantus Product. Pet. Mot. to Exclude, 1–2. Exhibit 2051 is an Order from the related Delaware litigation, and Exhibit 2052 is a compilation of excerpts from the trial transcript in that same litigation. *Id.* at 2–4. Petitioner moves to exclude Exhibits 2042–2045 as irrelevant and prejudicial under Federal Rules of Evidence ("FRE") 402 and 403, and as improper summaries under FRE 1006. *Id.* at 1–2. Petitioner moves to exclude Exhibits 2051–2052 as irrelevant and prejudicial under FRE 402 and 403, and further moves to exclude Exhibit 2052 as an improper summary under FRE 1006. *Id.* at 2–3. Patent Owner opposes. Paper 64.

We do not rely on any of Exhibits 2042–2045 or Exhibits 2051–2052 in making our ultimate determination on the patentability of the challenged claims. Accordingly, we need not decide Petitioner's Motion to Exclude those exhibits, and we dismiss the motion as moot.

2. Patent Owner's Motion to Exclude

Patent Owner moves to exclude the following exhibits, or portions thereof: Exhibits 1144–1161; Exhibit 1111; Exhibit 1169 ¶¶ 13–14, 40–49; Exhibit 1174; Exhibit 1181 ¶¶ 15–16, 18–24, 26, 28, 30–36, 38–51, 53–56; Exhibit 1114; and Exhibits 1057–1058. Paper 61 ("Patent Owner Mot. to Exclude"). Patent Owner notes that the exhibits fall into several categories: (a) documents and testimony related to Patent Owner's confidential information; (b) testimony from witnesses that Patent Owner alleges lack the scientific, technical, or other specialized knowledge required under Federal Rule of Evidence 702; (c) testimony that is not cited in the Petition or Reply; and (d) evidence that Patent Owner alleges is inadmissible hearsay. *Id.* We address each category below.

a. Documents and testimony related to Patent Owner's confidential information

Patent Owner moves to exclude Exhibits 1144–1161 and Dr. Langer's declaration (Ex. 1111) in its entirety. Patent Owner Mot. to Exclude 5–10. Patent Owner argues that we should exclude Exhibits 1144–1161 under FRE 402 and 403 because confidential information is irrelevant to the knowledge of an ordinarily skilled artisan. *Id.* at 5–7. Patent Owner argues that we should exclude Dr. Langer's declaration under FRE 702 because his opinions regarding obviousness are compromised by his reliance on Patent Owner's confidential documents. *Id.* at 7–10. Although Patent Owner seeks to exclude Dr. Langer's declaration in its entirety, Patent Owner identifies only certain paragraphs of the declaration as containing or relying upon the confidential information. *See id.* at 7–8 (identifying paragraphs 117–126, 130–145, 148, 149, 163–165, 168–172, and 177 of Dr. Langer's declaration). Petitioner opposes, arguing that it does not offer the exhibits as prior art, but rather, to refute Patent Owner's argument that an

ordinarily skilled artisan would not have viewed the prior art the way the Petition proposes. Paper 67, 1–2. Petitioner contends that such evidence is relevant to the credibility of Patent Owner's positions and Dr. Trout's testimony. *Id.* at 2.

We deny Patent Owner's request to exclude the entirety of Dr. Langer's declaration because Patent Owner's arguments go to the weight we should accord Dr. Langer's testimony and Dr. Langer's credibility, not the declaration's admissibility. *See, e.g.*, *Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co.*, Case CBM2012-00002, slip op. at 70 (Paper 66) (PTAB Jan. 23, 2014) ("[T]he Board, sitting as a non-jury tribunal, is well-positioned to determine and assign appropriate weight to the evidence presented in this trial, without resorting to formal exclusion that might later be held reversible error."). Further, although Patent Owner moves to exclude Dr. Langer's declaration under FRE 702, Patent Owner's motion does not discuss why the declaration is inadmissible under that rule.

As to Exhibits 1144–1161 and paragraphs 117–26, 130–45, 148, 149, 163–65, 168–72, and 177 of Dr. Langer's declaration, we do not rely on any of that evidence in making our ultimate determination on the patentability of the challenged claims. Accordingly, we need not decide Patent Owner's motion as to those exhibits and paragraphs, and we dismiss that portion of Patent Owner's motion as moot.

b. Testimony from witnesses that allegedly lack the knowledge required under Federal Rule of Evidence 702

Patent Owner moves to exclude paragraphs 40–43 of Dr. McDuff's declaration (Ex. 1169) and the entirety of Dr. Biggs' declaration (Ex. 1174), arguing that the testimony lacks the scientific, technical, or other specialized

knowledge that FRE 702 requires. Patent Owner Mot. to Exclude 10–13. Petitioner opposes. Paper 67, 5–6.

We do not rely on Dr. Biggs' declaration or any of paragraphs 40–43 of Dr. McDuff's declaration in making our ultimate determination on the patentability of the challenged claims. Accordingly, we need not decide Patent Owner's motion as to those exhibits and paragraphs, and we dismiss that portion of Patent Owner's motion as moot.

c. Testimony not cited in the Petition or Reply

Patent Owner moves to exclude portions of Dr. Langer's, Dr. McDuff's, Dr. Biggs' declarations, as well as portions of Dr. Yalkowsky's reply declaration and Exhibit 1114 as irrelevant under FRE 403 because Petitioner did not cite that evidence in its Petition or Reply. Patent Owner Mot. to Exclude 14. Petitioner opposes. Paper 67, 8–9.

As to Exhibit 1114, we do not rely on that evidence in making our ultimate determination of the patentability of the challenged claims. Accordingly, we need not decide Patent Owner's motion as to that exhibits, and we dismiss that portion of Patent Owner's motion as moot.

Turning to the expert declarations, although Patent Owner cites *SK Innovation Co., Ltd. v. Celgard, LLC*, Case IPR2014-00679, slip op. at 49 (Paper 58) (PTAB Sept. 25, 2015) as supporting exclusion of certain information, we do not agree. First, we note that *SK Innovation* is not precedential and, therefore, not binding. Moreover, in *SK Innovation*, the Board excluded exhibits—not portions thereof—that a party did not cite during the course of the proceeding. Here, Petitioner cites to and relies upon each declaration exhibit its Reply. Accordingly, we deny Patent Owner's motion as to those declarations.

d. Allegedly inadmissible hearsay evidence

Patent Owner moves to exclude paragraphs 20–22 and 25–30 of Dr. Biggs' declaration (Ex. 1174) and Exhibits 1057–1058 under FRE 802 as containing inadmissible hearsay. Patent Owner Mot. to Exclude 13, 15. Petitioner opposes. Paper 67, 7–8, 10.

We do not rely on paragraphs 20–22 and 25–30 Dr. Biggs' declaration or Exhibits 1057–1058 in making our ultimate determination on the patentability of the challenged claims. Accordingly, we need not decide Patent Owner's motion as to those paragraphs and exhibits, and we dismiss that portion of Patent Owner's motion as moot.

In sum, we deny-in-part and dismiss-in-part as moot Patent Owner's Motion to Exclude.

III. DISCUSSION OF UNPATENTABILITY CHALLENGES

Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). To prevail, Petitioner must establish the facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). Below, we explain how Petitioner has met its burden with respect to the challenged claims.

C. *Principles of Law*

Obviousness is a question of law based on underlying determinations of fact. *Graham v. John Deer Co.*, 383 U.S. 1, 17 (1966); *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479. The underlying factual determinations include: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective

evidence of nonobviousness, i.e., secondary considerations. *See Graham*, 383 U.S. at 17–18. Subsumed within the *Graham* factors are the requirements that all claim limitations be found in the prior art references and that the skilled artisan would have had a reasonable expectation of success in combining the prior art references to achieve the claimed invention. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). "Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–4 (Fed. Cir. 1988).

Moreover, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417.

D. *Level of Ordinary Skill in the Art*

We consider each asserted ground of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends that, as of June 2002, a person of ordinary skill in the art would have had "an M.S. or Ph.D. or equivalent in pharmacology, pharmaceutical sciences, or a closely related field; or an M.D. with practical academic or industrial experience in peptide injection formulations or stabilizing agents for such formulations." Pet. 14 (citing Dr. Yalkowsky's testimony, Ex. 1003 ¶¶ 31–34). As an example, Petitioner notes and Dr. Yalkowsky testifies, that a person of ordinary skill in the art would have had experience in surfactants that are commonly used in peptide injection formulations and an understanding of the factors that contribute to the molecule's instability. *Id.*; Ex. 1003 ¶ 33. Petitioner further contends that an ordinary artisan may have "consulted with one or more team members of experienced professionals

to develop an insulin formulation resistant to the well-known aggregation propensities of insulin molecules." Pet. 14–15; *see* Ex. 1003 ¶ 34.

Patent Owner does not offer a separate description for one of ordinary skill in the art. Nevertheless, Patent Owner disputes some aspects of Petitioner's description of the level of ordinary skill in the art. Resp. 19–21. Specifically, Patent Owner contends that Petitioner: (1) describes the field of invention improperly; (2) asserts that the skilled artisan would have been more than ordinarily creative by consulting other team members; and (3) incorrectly suggests that a person of ordinary skill in the art "would have been aware of or expected that the original LANTUS glargine formulation would be prone to aggregation under normal use conditions." *Id.* at 19–20.

The parties' disputes about the person of ordinary skill in the art appear to be directed to an issue at the heart of this case—what an ordinarily skilled artisan would have expected as to aggregation of insulin glargine. We need not—and do not—decide that issue as part of determining the level of ordinary skill in the art. We find that a person of ordinary skill in the art would have possessed an M.S., a Ph.D., or equivalent in pharmacology, pharmaceutical sciences, or a closely related field; or an M.D. with practical academic or industrial experience in peptide injection formulations or stabilizing agents for such formulations. We further find that a person of ordinary skill in the art would have understood instabilities that affect proteins in formulation, and that proteins may aggregate. *See* Ex. 1003 ¶ 33; Ex. 2006 ¶ 34. This description is consistent with the level of ordinary skill in the art at the time of the invention as reflected in the prior art in this proceeding. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect the appropriate level of ordinary skill in art).

Further, based on Petitioner's and Patent Owner's experts' statements of qualifications and curriculum vitae, we find that Dr. Yalkowsky, Dr. Langer, and Dr. Trout[7] are qualified to opine from the perspective of a person of ordinary skill in the art at the time of the invention. *See* Ex. 1003, Ex. A (Dr. Yalkowsky's curriculum vitae); Ex. 1111A (Dr. Langer's curriculum vitae); Ex. 2007 (Dr. Trout's curriculum vitae).

E. *Claim Construction*

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b) (2016)[8]; *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, claim terms are given their ordinary and customary meaning in view of the specification, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set

[7] The parties do not offer their additional witnesses as persons of ordinary skill in the art. Petitioner offers Dr. Biggs as a fact witness. Tr. 25:11–26:5. And Petitioner and Patent Owner offer Dr. McDuff and Dr. Baker, respectively, not as persons of ordinary skill in the art, but as economic experts to opine on the commercial success of Patent Owner's reformulated Lantus product. *See* Ex. 1169 ¶¶ 1–5, 7 (detailing Dr. McDuff's qualifications scope of work); Ex. 2039 ¶¶ 1–5, 8 (detailing Dr. Baker's qualifications and assignment).

[8] The Office recently changed the claim construction standard applicable to an *inter partes* review. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018). The rule changing the claim construction standard, however, does not apply to this proceeding because Petitioner filed its Petition before the effective date of the final rule, i.e., November 13, 2018. *Id.* at 51,340 (rule effective date and applicability date), 51,344 (explaining how the Office will implement the rule).

forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

We determined in the Institution Decision that no claim term required express construction based on the record developed at that stage of the proceeding. Inst. Dec. 9. Neither party contests our decision not to expressly construe claim terms. *See* Resp. 18–19; *see generally* Reply. On the full record before us, we can determine the patentability of the challenged claims without expressly construing any claim term. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("only those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy").

F. *Summary of Asserted References*

Before turning to the instituted grounds, we provide a brief summary of the asserted references.[9]

1. Lantus Label (Ex. 1004)

Lantus Label describes the commercially available Lantus formulation, a solution of insulin glargine (21^{A}-Gly-30^{B}-a-L-Arg-30^{B}-b-L-Arg-human insulin) "a recombinant human insulin analog that is long-acting (up to 24-hr duration of action)" and "produced by recombinant DNA technology." Ex. 1004, 3. The Lantus formulation is prescribed for injection and "consists of insulin glargine dissolved in a clear aqueous fluid." *Id.* Each milliliter of Lantus contains 100 IU insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection. *Id.* The pH of Lantus is approximately 4, and is adjusted by adding

[9] Although we refer to the original pagination associated with each reference in footnotes 1–5, setting forth the full citation of the references, we refer in our discussion to the pagination Petitioner added to each reference.

aqueous solutions of hydrochloric acid and sodium hydroxide to the formulation. *Id.*

Lantus Label also describes the pharmacodynamics of Lantus, explaining that Lantus is "completely soluble" at pH 4, but "[a]fter injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released." *Id.* As a result, Lantus has a relatively constant concentration/time profile, which allows once-daily dosing. *Id.*

Lantus Label instructs that Lantus "must only be used if the solution is clear and colorless with no particles visible." *Id.* at 5; *see also id.* at 6 ("You should look at the medicine in the vial. If the medicine is cloudy or has particles in it, throw the vial away and get a new one.").

2. Owens (Ex. 1005)

Owens describes clinical studies designed to determine the subcutaneous absorption rates of insulin glargine with 15, 30, and 80 µg/ml zinc. Ex. 1005, 1. Owens teaches that insulin glargine is "a di-arginine (30^{B}a-L-Arg-30^{B}b-L-Arg) human insulin analog in which asparagine at position 21^{A} is replaced by glycine." *Id.* Owens discloses that such a replacement "achieves an increase in the isoelectric point from pH 5.4 (native insulin) to 7.0 and stabilization of the molecule. When injected as a clear acidic solution (pH 4.0), insulin glargine undergoes microprecipitation in the subcutaneous tissue, which retards absorption." *Id.*

In one of the studies, Owens administers subcutaneously, from 5-ml vials, a formulation containing 100 IU/ml insulin glargine[15] or insulin glargine[80], m-cresol, and glycerol at pH 4.0, with 15 and 80 µg/ml zinc, respectively. *Id.* at 3. In

another study, Owens administers subcutaneously a formulation containing 100 IU/ml insulin glargine, 30 µg/ml zinc, m-cresol, and glycerol at pH 4.0. *Id.* at 4.

3. Lougheed (Ex. 1006)

Lougheed explains that "the tendency of insulin to aggregate during storage in and delivery from [infusion] devices remains one of the fundamental obstacles to their prolonged clinical use." Ex. 1006, 1. In an attempt to address that obstacle, Lougheed describes studies carried out to determine "the effects of physiologic and nonphysiologic compounds on the aggregation behavior of crystalline zinc insulin (CZI) solutions." *Id.* In those studies, Lougheed tested anionic, cationic, and nonionic surfactants, "in view of their known protein-solvation characteristics and their potential to constrain the conformation of insulin[ ] . . . in aqueous solution[,]" to determine whether such surfactants stabilized CZI solutions against aggregation. *Id.* at 1–2. Specifically, Lougheed subjected CZI solutions that contained the surfactants to continuous rotation or shaking to determine whether the surfactants enhanced stability of the CZI solutions as compared to a control of insulin in distilled water. *Id.* at 3. Lougheed describes the formulation stabilities (FS) of the solutions in terms of continuous rotation (FSR) or shaking (FSS). *Id.*

Lougheed reports that Tween 20, Tween 80, and other "nonionic and ionic surfactants containing the hydrophobic group, $CH_3(CH_2)_N$, where N = 7–16, remarkably stabilized CZI formulations while those lacking such groups demonstrated little or no effect." *Id.* at 1. In Table 3, Lougheed shows the stabilities of formulations containing Tween 20, Tween 80, and other nonionic surfactants. *Id.* at 3–4. Table 3 demonstrates that Tween 20 had an FSR value of 68 days, while Tween 80 had an FSR value of 48 days, as compared to 10 days for the insulin control solutions. *Id.* at 3. Lougheed concludes from the stability data

that the nonionic surfactants inhibited aggregate formation in the CZI solution. *Id.*; *see also id.* at 7 (explaining that the nonionic surfactants "markedly increased the stability of their respective formulations when these were subjected to continuous rotation at 37°C").

4. FASS (Ex. 1007A)

FASS describes Insuman Infusat insulin, which is administered as a subcutaneous, intravenous, or intraperitoneal infusion with an insulin pump for the treatment of diabetes mellitus. Ex. 1007A, 5. Each milliliter of the injectable solution contains 100 IU of biosynthetic insulin, 0.058 mg zinc chloride, 6 mg trometamol, 20 mg glycerol, 0.01 mg poly(oxyethylene, oxypropylene)glycol, 2.7 mg phenol (a preservative), 3.7 mg hydrochloric acid, and up to 1 ml water. *Id.* FASS discloses that poly(oxyethylene, oxypropylene)glycol is a stabilizer in the formulation that "prevents precipitation and flocculation of the insulin." *Id.* at 7.

5. Grau (Ex. 1008)

Grau explains that insulin stability "has been a significant impediment in the development of mechanical medication-delivery devices for diabetes," pointing to the tendency of insulin to "precipitate, aggregate in high-molecular-weight forms, and denature." Ex. 1008, 1. Searching for an insulin preparation to overcome that obstacle, Grau studies the ability of Genapol, a polyethylene-polypropylene glycol, to inhibit insulin aggregation in pump catheters. *Id.*

For the study, Grau uses a "pH-neutral buffered insulin formulation containing either 100 or 400 IU/ml semi-synthetic human insulin [], 27.8 or 111 µg/ml zinc ions (for U-100 and U-400 insulin, respectively) with 2 mg/ml phenol as a preservative, 16 mg/ml glycerol as an isotonicity agent, 50 mM of tris-(hydroxymethyl)-aminomethane (Tris) buffer, and 10 µg/ml polyethylene-polypropylene glycol (Genapol, Hoechst AG, Frankfurt, FRG)." *Id.* Grau tests the

insulin formulations in two ways: (1) on a shaking apparatus in a programmable implantable medication system ("PIMS"); and (2) *in vivo* in dogs implanted with the PIMS devices. *Id.* at 2–3. The PIMS devices include a fluid handling system through which the insulin travels, making contact with titanium metal surfaces and the catheter tubing. *Id.* at 2.

Grau analyzes the insulin using scanning electron microscopy and x-ray microanalysis (for the PIMS mounted on the shaking apparatus) or high performance liquid chromatography (for implanted PIMS). *Id.* at 3. Grau reports that changes to the Genapol formulations after testing were "comparable to those seen in insulin stored in a glass vial at 37°C without movement," and that the surfaces of the PIMS devices "were clean of apparent precipitate even in remote corners." *Id.* at 4–5. Grau concludes that "Genapol, a surface-active polyethylene-polypropylene glycol, effectively prevents adsorption of insulin to hydrophobic surfaces . . . . The data demonstrate good stability in accelerated laboratory tests and after as long as 5 mo between refills in vivo." *Id.* at 6.

G. *Patentability Analysis*

Below, we discuss whether Petitioner demonstrates, by a preponderance of the evidence, that the challenged claims are unpatentable as obvious over the asserted combinations of cited references.

1. The Limitations of the Challenged Claims

Petitioner contends that the asserted references in each ground teach each and every limitation of the challenged claims. *See* Pet. 25–60. Patent Owner does not dispute Petitioner's contentions in that regard. *See generally* Resp. We find that Petitioner establishes, by a preponderance of the evidence, that the references asserted in each ground collectively teach each limitation of the claims challenged in that ground.

a. Grounds 1 and 4: Lantus Label or Owens and Lougheed collectively teach or suggest each limitation of claims 1–25

Petitioner asserts that Lantus Label or Owens teaches every limitation of independent claims 1, 7, and 24, except for "at least one chemical entity chosen from polysorbate 20 and polysorbate 80," as recited in claim 1, or "at least one chemical entity chosen from polysorbate and poloxamers," as recited in claims 7 and 24. Pet. 25–26, 29–30 (discussing Lantus Label and citing Ex. 1001, 4:27–28; Ex. 1003 ¶¶ 98–102, 129, 160–162, 175–180; Ex. 1004, 3), 45–48 (discussing Owens and citing Ex. 1001, 4:27–28; Ex. 1003 ¶¶ 98–102, 239; Ex. 1005, 3–4). For those limitations, Petitioner points to Lougheed's teaching of adding polysorbate 20 (Tween 20) or polysorbate 80 (Tween 80) to insulin formulations. *Id.* at 26, 30, 45–47 (citing Ex. 1003 ¶¶ 163–169, 175–180, 242, 251–252; Ex. 1006, 4, 7, Table 3). Petitioner makes similar assertions regarding the limitations of the dependent claims, relying on the disclosure of Lantus Label (Ground 1) or Owens (Ground 4) or Lougheed (Grounds 1 and 4) for teaching the additional limitations of those claims. *See id.* at 31–33, 37–39, 48–50, 52–54, 55–56 (relying on Lougheed for teaching the additional limitations of claims 2, 8, 13, 14, 17–19, 21, and 22); *id.* at 33–36, 39–41 (relying on Lantus Label for teaching the additional limitations of claims 3–6, 9–12, 15, 16, 20, 23, and 25); *id.* at 50–52, 54–55 (relying on Owens for teaching the additional limitations of claims 3–6, 9–12, 15, 16, 20, and 23).

Patent Owner does not challenge Petitioner's showing or evidence that Lantus Label and Lougheed or Owens and Lougheed teach or suggest each limitation of claims 1–25. *See generally* Resp.[10]

[10] Patent Owner also does not challenge Petitioner's assertions that Lantus Label, Owens, and Lougheed are prior art printed publications. *See generally id.*

Based on the full trial record, we find that Lantus Label and Lougheed, as well as Owens and Lougheed, collectively teach or suggest each limitation of the challenged claims. Specifically, we find that Lantus Label or Owens teaches every limitation of independent claims 1, 7, and 24, except for the limitation of "at least one chemical entity chosen from polysorbate 20 and polysorbate 80," as recited in claim 1, or "at least one chemical entity chosen from polysorbate and poloxamers," as recited in claims 7 and 24. Ex. 1004, 3; Ex. 1005, 3–4; *see* Ex. 1003 ¶¶ 129–131 160–62, 175–80, 239. As explained above, Lantus Label describes the commercially available Lantus formulation, which is a solution of insulin glargine (21^{A}-Gly-30^{B}-a-L-Arg-30^{B}-b-L-Arg-human insulin) for injection. Ex. 1004, 3. Each milliliter of Lantus contains 100 IU insulin glargine, 30 mcg zinc, 2.7 mg m-cresol (a preservative), 20 mg glycerol 85%, and water for injection. *Id.* The pH of Lantus is approximately 4. *Id.* Owens describes insulin glargine formulations containing 100 IU/ml insulin glargine[15] or insulin glargine[80], m-cresol, and glycerol at pH 4.0, with 15 and 80 µg/ml zinc, respectively. Ex. 1005, 3.

We also find that Lougheed teaches adding polysorbate 20 (Tween 20) or polysorbate 80 (Tween 80) to insulin formulations. Ex. 1006, 4, 7, Table 3; Ex. 1003 ¶¶ 163–169, 175–180. And we find that Lantus Label (Ground 1), Owens (Ground 4) or Lougheed (Grounds 1 and 4) teach or suggest the additional limitations of dependent claims 2–6, 8–23, and 25. *See* Pet. 31–41, 45–56; Ex. 1003 ¶¶ 182–184, 197, 204, 208–209, 212, 216, 220, 260, 255–257, 264–265, 268–269, 273–275, 277–278, 285–287, 289–292, 294–295; Ex. 1004, 3; Ex. 1005, 3–4; Ex. 1006, 4–7, Tables 3–6. Accordingly, Petitioner demonstrates, by a preponderance of the evidence, that Lantus Label and Lougheed, and Owens and Lougheed, collectively teach each and every limitation of claims 1–25.

b. Grounds 2, 3, 5, and 6: Lantus Label and FASS or Grau, and Owens and FASS or Grau collectively teach each limitation of claims 7 and 24

Petitioner asserts that Lantus Label and FASS (Ground 2) or Grau (Ground 3) collectively teach each limitation of claims 7 and 24. Pet. 41–45. Petitioner further asserts that Owens and FASS (Ground 5) or Grau (Ground 6) collectively teach each limitation of claims 7 and 24. Pet. 56–60. Petitioner's arguments as to how the references collectively teach each limitation are substantially the same as those for claims 7 and 24 in Ground 1 (based on Lantus Label and Lougheed), except that Petitioner cites FASS or Grau instead of Lougheed for Grounds 2, 3, 5, and 6, and Petitioner cites Owens instead of Lantus Label for Grounds 5 and 6.

For Grounds 2 and 3, Petitioner argues that Lantus Label teaches all of the elements of claims 7 and 24, except that Lantus Label does not teach "at least one chemical entity chosen from polysorbate and poloxamers," as recited in both claims. Pet. 41–42 (Lantus Label and FASS), 43 (Lantus Label and Grau). For that limitation in Ground 2, Petitioner directs us to FASS' teaching that adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer) to an insulin formulation "prevents precipitation and flocculation of the insulin," which makes the formulation "particularly suited for use in insulin pumps." *Id.* at 42 (quoting Ex. 1007A, 7); *see id.* (citing Ex. 1033A, 6). For that limitation in Ground 3, Petitioner directs us to Grau's teaching of adding a poloxamer (Genapol) to insulin formulations "to inhibit insulin aggregation" for various *in vitro* and *in vivo* tests with PIMS devices. *Id.* at 43–44 (citing Ex. 1008, 2–6).

For Grounds 5 and 6, Petitioner argues that Owens teaches all of the limitations of claims 7 and 24, except that Owens does not teach "at least one chemical entity chosen from polysorbate and poloxamers," as recited in both claims. Pet. 56–57 (Owens and FASS), 58–59 (Owens and Grau). For that limitation in Ground 5, Petitioner directs us to FASS' teaching that adding the

stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer) to an insulin formulation "prevents precipitation and flocculation of the insulin," which makes the formulation "particularly suited for use in insulin pumps." *Id.* at 57 (quoting Ex. 1007A, 7); *see id.* (citing Ex. 1033A, 6). For that limitation in Ground 6, Petitioner directs us to Grau's teaching of adding a poloxamer (Genapol) to insulin formulations "to inhibit insulin aggregation" for various *in vitro* and *in vivo* tests with PIMS devices. *Id.* at 58–59 (citing Ex. 1008, 2–6).

Patent Owner does not challenge Petitioner's showing or evidence that Lantus Label and FASS or Grau, and Owens and FASS or Grau teach or suggest each limitation of claims 1–25. *See generally* Resp.[11]

As explained above, based on the full trial record, we find that Lantus Label or Owens teaches every limitation of claims 7 and 24, except for the limitation requiring "at least one chemical entity chosen from polysorbate and poloxamers." *See supra* § III.E.1.a; Ex. 1004, 3; Ex. 1005, 3–4; *see also* Ex. 1003 ¶¶ 129, 160–162, 175–180, 223, 239 (Dr. Yalkowsky's testimony regarding the teachings of Lantus Label and Owens, which we credit). We further find that FASS and Grau teach adding a poloxamer to insulin formulations. Specifically, FASS teaches adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer) to an insulin formulation (Ex. 1007A, 7), and Grau teaches adding the poloxamer Genapol to insulin formulations (Ex. 1008, 2–6). *See also, e.g.*, Ex. 1003 ¶¶ 224, 232 (Dr. Yalkowsky's testimony regarding the teachings of FASS and Grau, which we credit). Thus, Petitioner demonstrates, by a preponderance of the evidence, that Lantus Label and FASS or Grau, and the collective teachings of Owens and FASS or Grau, collectively teach each and every limitation of claims 7 and 24.

[11] Patent Owner also does not challenge Petitioner's additional assertions that FASS and Grau are prior art printed publications. *See generally id.*

2. Reason to Modify Lantus Label's and Owens's Insulin Glargine Formulations to Include Nonionic Surfactants and Reasonable Expectation of Success

A patent "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Petitioner must also demonstrate that one of ordinary skill in the art would have had a reason to combine the prior art elements to achieve the claimed invention with a reasonable expectation of success. *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1183 (Fed. Cir. 2014). These factors are subsidiary requirements for obviousness subsumed within the *Graham* factors. *Pfizer*, 480 F.3d at 1361.

a. Petitioner's assertions

Petitioner argues that a skilled artisan would have had several reasons to include a surfactant, such as the polysorbates that Lougheed teaches or the poloxamers that FASS and Grau teach (collectively, "nonionic surfactants"), in the insulin glargine formulations that Lantus Label and Owens teach. First, Petitioner asserts it was well-known in the art that insulins had a tendency to aggregate upon storage and delivery. Pet. 26–28 (citing Ex. 1001, 3:2–6; Ex. 1003 ¶¶ 163–169; Ex. 1006, 1). As support, Petitioner points to, *inter alia*, Lougheed's teaching that "the tendency of insulin to aggregate during storage in and delivery from . . . devices remains one of the fundamental obstacles to their prolonged clinical use." Ex. 1006, 1; *see* Pet. 26. Petitioner also identifies what it contends are known insulin aggregation factors, including contact with air present in the vials used to store the insulin glargine, the hydrophobic surfaces of the glass vials and rubber stopper material of the vial seals, insulin glargine's acidic pH environment, and the presence of monomers in the insulin glargine solution. Pet. 6–7, 13 (citing Ex. 1001, 3:2–14; Ex. 1003 ¶¶ 105–123, 126; Ex. 1015, 3); *see* Ex. 1003 ¶¶ 105–

108, 126 (citing Ex. 1014, 9; Ex. 1015, 3–4, 6; Ex. 1018, 1, 8 Ex. 1031, 1); Reply 5 (citing Ex. 1181 ¶¶ 9, 25).

Second, Petitioner contends that:

> It is beyond reasonable dispute that non-ionic surfactants were used in commercially-available insulin formulations for inhibiting protein aggregation long before the priority date of the '652 patent's claims. Thus a PHOSITA would have had reason to improve commercially-available insulin glargine formulations (*see*, *e.g*, LANTUS® 2000 label [Ex. 1004] and Owens [Ex. 1005]) by anti-aggregation additives, such as Brij 35, Lubrol WX, Triton X100, Tween 20, Tween 80, poloxamer 171, poloxamer 181 and other known surfactants, which were used routinely to inhibit aggregation and formation of particles in peptide and protein-containing formulations.

Pet. 10 (citing Ex. 1003 ¶ 128). Petitioner points to Lougheed's disclosure that surfactants, such as polysorbate 20 and polysorbate 80 enhance the stability of insulin formulations and decrease insulin aggregation. *Id.* at 26 (citing Ex. 1003 ¶¶ 163–169; Ex. 1006, 4, 7, Table 3). Petitioner also explains that FASS and Grau teach surfactants (poloxamers) to enhance the stability of insulin formulations and inhibit insulin aggregation. *Id.* at 57–59 (citing Ex. 1007A, 7; Ex. 1008, 2–5).

Third, Petitioner asserts that Lantus Label explicitly warns patients not to use the product if aggregation occurs such that Lantus Label itself would have provided a reason to modify the insulin glargine formulation. *Id.* at 27 (citing Ex. 1004, 5–6).

Petitioner further asserts that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed formulations because surfactants, such as polysorbates, "were commonly used to stabilize other protein and peptide formulations well prior to June 2002[,]" and already were included in the Food and Drug Administration Inactive Ingredients Guide for various pharmaceutical formulations. *Id.* at 26–27 (citing Ex. 1003 ¶¶ 163–169,

172; Ex. 1016, 3, Table I). Thus, argues Petitioner, a person of ordinary skill in the art "would have had ample reason" to add polysorbate 20, polysorbate 80, and/or a poloxamer to an insulin glargine formulation, "with a reasonable expectation that doing so would successfully inhibit or eliminate insulin's well-known propensity to aggregate." *Id.* at 27; *see, e.g.*, *id.* at 58–60 (citing Ex. 1003 ¶¶ 297–300, 302–306; Ex. 1005, 3; Ex. 1007A).

b. Patent Owner's assertions

Patent Owner responds that Petitioner fails to provide prior art evidence that glargine had a tendency to aggregate. Resp. 29–32. In that regard, Patent Owner argues that Lantus Label and Owens teach clear, soluble solutions that were stable in an acidic pH, and that Petitioner's reliance on the "use-only-when-clear" patient instructions in Lantus Label as conveying an aggregation problem is misplaced. *Id.* at 30–31 (citing 1004, 3; Ex. 1005, 1; Ex. 2006 ¶¶ 113–116; Ex. 2008, 30:17–31:10). Patent Owner also notes that the "use-only-when-clear" instruction is found in most labels for injectable drugs. *Id.* at 31 (citing Ex. 2006 ¶ 117). And Patent Owner explains that Petitioner's asserted references relate to chemical and physical instability of human and animal insulin formulations, not the modified, recombinant insulin glargine formulations. *Id.* at 31 (citing generally Ex. 1006; Ex. 1007A; Ex. 1008; Ex. 1014; Ex. 1015; Ex. 1018).

Patent Owner further responds that Petitioner fails to provide evidence that a person of ordinary skill in the art would have expected the same aggregation problem for insulin glargine, as was known for other insulins. Resp. 32–44. Patent Owner presents four arguments in that regard. First, Patent Owner argues a person of ordinary skill in the art would not have expected insulin glargine to aggregate based on prior art disclosing chemical and physical instability in human and animal insulin because insulin and insulin glargine have structural differences

resulting in changes in physical and chemical properties of insulin glargine. *Id.* at 33–38 (citing Ex. 2004, 2:51–61; 2006 ¶¶ 59–63, 76–78, 123–124, 148). Second, Patent Owner argues that the evidence of record does not support Petitioner's assertion that a person of ordinary skill in the art would have expected insulin glargine to aggregate due to the prevalence of monomers. *Id.* at 38–40 (citing Ex. 1011, 12; Ex. 1031, 1; Ex. 2006 ¶¶ 116, 136–138, 159; Ex. 2018, 1, 7). Third, Patent Owner argues that the prior art does not teach that insulin glargine formulations are prone to aggregation at acidic pH. *Id.* at 40–42. Fourth, Patent Owner argues that a skilled artisan would not have expected aggregation based on prior art related to insulin pumps (i.e., Lougheed, FASS, and Grau), because insulin for pump formulations "is a special case requiring stabilization that is not needed in other insulin formulations." *Id.* at 42–44 (citing Ex. 1006, 1; Ex. 1007A, 5; Ex. 1008, 1; Ex. 1015, 6; Ex. 2006 ¶¶ 65, 72–73, 96–97, 106–111, 140).

Patent Owner also argues that the statements in the '652 patent background section cannot be used to support a rationale to modify the insulin glargine formulations because the patent specification distinguishes between insulin and insulin glargine, does not admit that insulin glargine had a known tendency to aggregate, and "simply recites what was known in the art . . . regarding *insulin* aggregation." *Id.* at 44–46.

As to reasonable expectation of success, Patent Owner asserts that there is no support for Petitioner's argument that adding polysorbates and/or poloxamers to insulin glargine formulations would have been routine. Resp. 46–47. Patent Owner argues that Petitioner's position "ignores the unpredictability of protein formulation," *id.* at 47, and the competing considerations that must be taken into account when introducing an additional component into a formulation. *Id.* at 47–48 (citing Ex. 2003, 28–29; Ex. 2006 ¶¶ 43–45, 149–166). Similarly, Patent

Owner contends that Petitioner's analysis fails to address whether introducing a surfactant would interfere with insulin glargine's mechanism of action or efficacy. *Id.* at 49–51. Patent Owner also argues that Petitioner fails to account for the potential negative consequences of adding a nonionic surfactant to the Lantus Label and Owens insulin glargine formulations. *Id.* at 52–56. According to Patent Owner those negative consequences "could" include polysorbate hydrolysis in acidic environments, discoloration of the formulation, interference with the antimicrobial properties and hexamer-stabilizing effects of m-cresol, and the potential for polysorbate to undergo autoxidation reactions during storage to form harmful peroxides in the formulation. *Id.* (citing Ex. 1012, 1; Ex. 1013; Ex. 1019, 5, 30, 41, 43, 46, 50; Ex. 2006 ¶¶ 153–166; Ex. 2015, 4; Ex. 2017, 1; Ex. 2028, 4).

c. Analysis

Turning first to reason to combine, we disagree with Patent Owner that, to meet its burden as a matter of law, Petitioner must provide prior art evidence that insulin glargine had a tendency to aggregate. Resp. 29–32. The prior art need not expressly articulate or suggest that insulin glargine had a tendency to aggregate. Rather, "a patent claiming the combination of elements of prior art" may be shown to be obvious if "the improvement is [no] more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 517. Here, Petitioner asserts that a person of ordinary skill in the art would have understood that aggregation generally was a concern in developing insulin formulations and that a surfactant predictably would have been added to the formulations to address that concern. Pet. 6–7, 24, 27–28. Based on our review of the full trial record, we find that Petitioner demonstrates a reason to modify the prior art, as explained below.

The '652 patent explains that insulins had a known tendency to aggregate in the presence of hydrophobic surfaces that come into contact with insulin formulations, such as "the glass vessels of the preparations, the stopper material of the sealing caps or the boundary surface of the solution with the air supernatant." Ex. 1001, 3:8–14. The '652 patent further states it was known that "very fine silicone droplets can function as additional hydrophobic aggregation nuclei in the taking of the daily insulin dose by means of customary, siliconized insulin syringes and accelerate the process." *Id.* at 3:14–17. The '652 patent does not exclude insulin glargine when describing the tendency for insulins to aggregate due to interactions with hydrophobic surfaces on vials and insulin delivery devices, including syringes. *See id.* at 3:2–17. And the record supports that an ordinarily skilled artisan would not have suspected insulin glargine to behave differently than other insulins, due to the differences in amino acids between them, when exposed to hydrophobic surfaces. For example, although bovine, porcine, and human insulin are structurally different, they all were known to aggregate (albeit to different degrees). Ex. 1014, 3 (Figure 1 depicting the primary structure of human insulin and noting that porcine insulin differs by one amino acid and bovine insulin differs by three amino acid); Ex. 1015, 2 (recognizing that human, porcine, and bovine all aggregate, but explaining that bovine insulin has a greater tendency to aggregate than human and porcine insulin).

The '652 patent also does not suggest that aggregation due to hydrophobic surfaces occurred only in pumps, as Patent Owner argues. To the contrary, as noted above, the '652 patent describes the hydrophobic surfaces of glass storage vials, stopper materials of sealing caps, the air-water interface, and siliconized daily use syringes as promoting aggregation. Additional evidence of record is consistent with the background of the '652 patent. *See* Ex. 1006, 1 (silicone rubber

promotes insulin aggregation); Ex. 1014, 8; Ex. 1015, 1 (insulin was known to undergo conformational changes when exposed to hydrophobic surfaces, such as the air/water interface in a vial, resulting in aggregation and the formation of a viscous gel or insoluble precipitates), 4; Ex. 1021, 1; Ex. 1026, 3 (insulin aggregates in glass vials); Ex. 2012, 9379 ("It has been suggested that insulin is destabilized at hydrophobic surfaces (air-water or water-pump materials)"). Thus, the background of the '652 patent and the prior art suggests that it is the air-water interfaces and interactions with hydrophobic surfaces that promote insulin aggregation, and not the type of device used to deliver the insulin formulation.

Given this evidence, we credit Dr. Langer's testimony that aggregation "was known in the art not to be unique to pumps," Ex. 1111 ¶ 92, over Dr. Trout's testimony that "[i]nsulin fibrillation was also known to be an issue confined to insulin pumps," Ex. 2006 ¶ 72. We further find that the evidence Dr. Trout cites does not support the conclusion that insulin aggregation was limited to pumps. *See id.* Rather, the evidence on which Dr. Trout relies indicates that insulin has a *greater tendency* to aggregate in pump delivery devices (i.e., a difference in degree) because it is exposed to a greater hydrophobic surface area. *See, e.g.*, Ex. 1008, 1 ("The problems associated with insulin use in implantable pumps are even greater").

The insulin glargine formulations in Lantus Label and Owens were supplied in vials—the same type of delivery materials that the '652 patent states were known to contain hydrophobic surfaces. *See* Ex. 1004, 6 (Lantus is supplied in 5mL and 10 mL vials); Ex. 1005, 3–4 (explaining that the insulin glargine formulations were administered from 5mL vials and injected subcutaneously). Further, it is not disputed that the vials in which the insulin glargine formulations were stored contained a "headspace" (air above the solution liquid) forming an air-

water interface. *See* Ex. 1037, 11 (depicting a 10 mL Lantus vial with stopper and air-water interface); Ex. 1054, 207:6–13, 207:22–208:21 (Dr. Trout's testimony that the headspace in the Lantus vials forming a gas-liquid interface). Thus, we find that a person of ordinary skill in the art would have been concerned about aggregation in the insulin glargine formulations that Lantus Label and Owens disclose.

Further, both parties' experts agree that insulins exist in equilibrium as monomers, dimers, and hexamers, which structure may affect its tendency to aggregate in solution. *See, e.g.*, Ex. 1003 ¶ 106 (citing Ex. 1018, 1); Ex. 2006 ¶¶ 55–56 (quoting Ex. 1018, 1 and citing Ex. 1014, 29). Certain factors such as pH, however, were known to shift the equilibrium toward the monomer, Ex. 1015, 3, whereas other factors, like the presence of zinc in the formulation, were known to promote hexamer formation, Ex. 1015, 7. *See* Ex. 2006 ¶ 68. As to pH, the background of the '652 patent states that "[e]specially at acidic pH, insulins . . . show a decreased stability and an increased proneness to aggregation on thermal and physicomechanical stress, which can make itself felt in the form of turbidity and precipitation (particle formation) (Brange et al., J. Ph. Sci. 86:517–525 (1997))." Ex. 1001, 3:2–7. And prior to the invention, a number of studies confirmed that although insulin was known to aggregate in neutral solutions, the rate of insulin aggregation increased in acidic solutions, due to the presence of more insulin monomers (than dimers and hexamers) in those solutions—monomers that unfolded exposing hydrophobic interfaces that were normally buried. *See* Ex. 1014, 9–10; Ex. 1015, 3, 6; Ex. 1018, 1; Ex. 2012, 9379.

As described in Lantus Label, insulin glargine was formulated as a clear solution with an acidic pH. Ex. 1004, 3 (Lantus formulation); *see also* Ex. 1001,

2:66–3:2 (describing background information). And Jones[12] described insulin glargine as "monomeric compared to pharmacological insulin preparations in which insulin is usually present as a hexamer." Ex. 1031, 1.

Patent Owner argues that, despite Jones's statement regarding the monomeric nature of insulin glargine, the evidence of record does not support Petitioner's assertion that insulin glargine was believed to have a greater proportion of monomers. Resp. 38–39. First, Patent Owner contends that Jones's statement is erroneous and based on a misreading of another reference that it cites—Hoogwerf.[13] Resp. 38–39. Patent Owner bases this argument on what it contends is a particular citation scheme that Jones adopts—citing references at the end of each paragraph, rather than at the end of each sentence. Tr. 54:19–55:5 (Patent Owner's counsel acknowledging that Jones's cite to Hoogwerf does not appear in the sentence on which Petitioner relies, but arguing that it applies to that sentence because Jones "does citations . . . at the end of paragraphs."). But Jones does not appear to employ that citation scheme. Indeed, many paragraphs include citations in the middle of sentences, or at the end of each sentence. Thus, we do not conclude on this record that Jones intended to cite Hoogwerf for the statement that insulin glargine is monomeric. Nor do we conclude that Jones's statement in that regard is erroneous. Rather, we consider Jones for what it would have taught the ordinary artisan—that insulin glargine is more monomeric than other insulin preparations.

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[12] Richard Jones, *Insulin glargine Aventis Pharma*, 3 IDRUGS 1081 (2000) (Ex. 1031). Although we refer to the original pagination associated with this reference in setting forth its full citation, we refer in our discussion to the page numbers Petitioner added to the reference.

[13] Hoogwerf et al., *Advances in the Treatment of Diabetes Mellitus in the Elderly – Development of Insulin Analogues*, 6 DRUGS & AGING 438–48 (1996) (Ex. 2018).

Patent Owner also contends that an ordinarily skilled artisan would have expected insulin glargine "to be more hexameric than insulin because [a]lterations to the molecule favor the formation of insulin hexamers" and because the insulin glargine formulations in Lantus Label and Owens include zinc, which was known to promote insulin hexamer formation. Resp. 39 (citing Ex. 1011, 2; Ex. 2006 ¶¶ 116, 159).

As to Patent Owner's argument regarding zinc, although we agree that the presence of zinc in a formulation was known to promote hexamer formation at neutral and basic pH, thus stabilizing the insulin in the formulation (Ex. 1003 ¶¶ 98, 100; Ex. 1168, 77; Ex. 2006 ¶ 57), it was also known that "in acidic solutions[,] insulin does not bind [zinc]" (Ex. 1168, 77.) As to Patent Owner's argument that insulin glargine's alterations favor hexamer formation, the fact that a chemical alteration favors hexamer formation, does not mean that insulin glargine is predominantly hexameric, especially given Jones's statement that insulin glargine is more monomeric than other insulins. Even assuming that insulin glargine is predominantly hexameric at acidic pH, however, prior art insulin formulations were believed to be hexameric at neutral pH, yet they still were known to aggregate at neutral pH. *See* Ex. 1006, 1 (aggregates formed in insulin preparations "even under normal storage conditions"), Ex. 1014, 8–10; Ex. 1018, 1 ("models have been proposed to describe the self-association [i.e., aggregation] of insulin in solution at both acidic and neutral pH"); Ex. 2012, 9377, 9379 (aggregation occurred in insulin formulations at pH 7). Thus, we find that a person of ordinary skill in the art would have had an additional reason to be concerned about aggregation in the insulin glargine formulations that Lantus Label and Owens disclose.

Turning to whether an ordinary artisan would have added nonionic surfactants to the insulin glargine formulations with a reasonable expectation of success, Patent Owner argues Petitioner's assertion that an ordinarily skilled artisan would have reasonably expected success in achieving the claimed pharmaceutical formulations "ignores the unpredictability of protein formulation" and the competing considerations that must be taken into account when introducing an additional component into a formulation. Resp. 47–48. Patent Owner's arguments regarding unpredictability of protein formulating are not persuasive under the proper legal inquiry regarding reasonable expectation of success. Under the proper inquiry, "obviousness cannot be avoided by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364.

Based on our review of the full trial record, Petitioner demonstrates, by a preponderance of the evidence, a reasonable probability of success. Specifically, the prior art is replete with examples of nonionic surfactants successfully used to stabilize insulins and other peptides against aggregation. As to insulin, Lougheed teaches formulations comprising insulin and surfactants, including nonionic surfactants (e.g., polysorbate 20 and polysorbate 80). *See* Ex. 1006, 2–3. Lougheed tested those surfactants as "stabilizers in view of their known protein-solvation characteristics and their potential to constrain conformation of insulin[] and other proteins in aqueous solution." *Id.* at 2. Lougheed concluded that the nonionic surfactants "markedly increased the stability of their respective formulations" under rotational testing. *Id.* at 7; *see also id.* at 3–4 (explaining that observed formulation stability continuous rotation values for insulin formulations including Tween 20 (i.e., polysorbate 20) and Tween 80 (i.e., polysorbate 80) are 68 days and 48 days, respectively, as compared with 10 days for insulin controls

(i.e., formulations that lacked surfactant additives). And FASS teaches that adding the stabilizer poly(oxyethylene, oxypropylene)glycol (i.e., a poloxamer) to an insulin formulation "prevents precipitation and flocculation of the insulin." Ex. 1007A, 7. Grau further teaches using nonionic surfactants to stabilize insulin formulations. Ex. 1008, 2–6 (adding a poloxamer (Genapol) to insulin formulations "to inhibit insulin aggregation" for various *in vitro* and *in vivo* tests with programmable implantable medication systems); *see also* Ex. 1111 ¶ 159 (Table 1, listing twenty prior art references describing surfactants used in insulin formulations, including two that disclose the use of polysorbates with insulin at acidic pH (e.g., Ex. 1023; Ex. 1125)).

Petitioner also directs us to a number of protein and polypeptide pharmaceutical formulations that include nonionic surfactants as stabilizers. Pet. 8–9; Ex. 1016, 3 (Table I listing a few of the approved surfactants, including polysorbate 20 and polysorbate 80); Ex. 1003 ¶¶ 111–123 (discussing several studies showing the stabilizing effect of nonionic surfactants on insulin, including Exs. 1023–1026). And Jones explains that nonionic surfactants "have been traditionally used in formulations to stabilize proteins." Ex. 1016, 2. These surfactants are attractive as additives in producing, purifying and stabilizing drugs because "many have already been approved for use internationally in medicinal products" and exhibit "low toxicity and low reactivity with ionic species." *Id.*

The prior art further discloses that nonionic surfactants such as Genapol (a poloxamer) successfully stabilized bovine, porcine, and human insulins, as well as three additional non-insulin proteins. Ex. 1021, 1, 3. Given the foregoing, we credit Dr. Yalkowsky's testimony that an ordinarily skilled artisan "would have indeed looked at the available protein formulations and what was acceptable to the [Food and Drug Administration ("FDA")]." Ex. 1181 ¶ 38; *see also* Ex. 1003

¶¶ 115 (explaining that the FDA had listed polysorbate 20 and polysorbate 80 as Generally Recognized As Safe ("GRAS") and they remain listed as GRAS). For the same reason, we find unpersuasive Patent Owner's arguments that an ordinarily skilled artisan would not have reasonably expected success when adding a nonionic surfactant to insulin glargine in view their success stabilizing other insulins and proteins. Resp. 46–51.

As noted previously, Patent Owner also argues that Petitioner fails to account for the potential negative consequences of adding a nonionic surfactant to the Lantus Label and Owens insulin glargine formulations. *Id.* at 52–56. This argument strikes us more as an argument directed to reason to modify and not reasonable expectation of success. To the extent Patent Owner's argument is so directed, we do not agree with Patent Owner that "potential" consequences would have discouraged an ordinary artisan from adding nonionic surfactants to the prior art glargine formulations. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("[A] given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine.").

Nor do we find that, based on the record as a whole, a person of ordinary skill in the art would have considered those potential consequences to have obviated a reasonable expectation of success in achieving the claimed formulations. For example, Patent Owner argues that an ordinarily skilled artisan would have been aware of the potential hydrolysis or saponification of polysorbate in acidic environments, given that "gradual saponification [of polysorbate] occurs with strong acids." Resp. 52–53 (citing Ex. 1019, 30, 50; Ex. 2006 ¶¶ 153–154). But Patent Owner does not direct us to evidence that a "strong acid" was or would have been present in the prior art Lantus formulations. *See id.*; Ex. 2006 ¶¶ 153–154. And Petitioner points to evidence that polysorbates were used in

pharmaceutical formulations at acidic pH. Reply 24; *see* Ex. 1139, 2 (disclosing Etoposide parenteral formulation that includes polysorbate 80 and has a pH of 3.0–4.0); Ex. 1054, 265:7–266:13).

Patent Owner also points to potential negative effects of using nonionic surfactants and phenols (e.g., cresol) in the same formulation. Resp. 53–55 (citing Ex. 1019, 30, 43, 50; Ex. 2006 ¶¶ 157–163). Petitioner, however, provides evidence that phenols and nonionic surfactants had been used together in pharmaceutical formulations. Reply 25 (and evidence cited therein); *see, e.g.*, Ex. 1141, 2 (disclosing Norditropin, a polypeptide hormone parenteral formulation that includes nonionic surfactant poloxamer 188 and phenol).

In sum, Petitioner demonstrates, by preponderance of the evidence, a reason that one of ordinary skill in the art would have modified the insulin glargine formulations that Lantus Label and Owens teach by adding nonionic surfactants to achieve the claimed pharmaceutical formulations with a reasonable expectation of success. That does not end our inquiry, however, because the record includes arguments and evidence regarding objective indicia of nonobviousness that we evaluate before making a final determination on obviousness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016).

3. Objective Indicia of Nonobviousness

Patent Owner argues that objective evidence of commercial success supports the nonobviousness of the challenged claims. Resp. 56–59. As explained further below, we are not persuaded that Patent Owner's arguments and evidence regarding commercial success support the nonobviousness of the challenged claims.

Patent Owner offers evidence of the success of the Lantus product. Resp. 57–59. Patent Owner explains that that original Lantus vial formulation exhibited

aggregation and precipitation during storage, "resulting in the normally clear formulation becoming visibly cloudy." *Id.* at 57. Patent Owner solved this problem by reformulating the original Lantus vial to include a nonionic surfactant "aimed at stabilizing the formulation without interfering with the glargine's unique profile of action." *Id.* Patent Owner asserts that the reformulated Lantus vial practices claims 1–12, 15–21, and 23–25 of the '652 patent. *Id.*

Patent Owner sells the reformulated Lantus vial, "with U.S. sales growing from $1.1 billion at its introduction to approximately $2.6 billion in 2017"—sales that "have accounted for approximately 33% of all sales of long-acting injectable insulin and/or insulin analog therapies." *Id.* at 57–58 (citing Ex. 2039 ¶¶ 29–30). Patent Owner contends that these sales amount to commercial success and that there is a nexus between the commercial success of the reformulated Lantus vial and the invention claimed in the '652 patent because the reformulated Lantus vial is the claimed invention. *Id.* at 58. Patent Owner further contends that a nexus exists because the reformulated Lantus vial "averted potential regulatory action and negative sales impacts that could have occurred had Patent Owner not remedied the aggregation issues with the original [Lantus] vial." *Id.* at 59 (citing Ex. 2006 ¶¶ 162–172; Ex. 2039 ¶¶ 36–39).

"When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *see WBIP*, 829 F.3d at 1329 (finding "a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent'"). That presumption of nexus,

however, is rebuttable, as "a patent challenger may respond by presenting evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention.'" *WBIP*, 829 F.3d at 1329.

There appears to be no dispute in this case that the Lantus product is a commercial success. *See* Reply 26 (arguing that "the commercial success of Lantus is attributable to the fact that it contains insulin glargine, not any non-ionic surfactants"). Petitioner, however, contends that any nexus between such success and the claimed invention is rebutted by, among other things, Patent Owner's failure "to account for its patent on the original insulin glargine compound, which blocked market entry of any competing insulin glargine products at least until after its expiration in September 2014." Reply 25–26 (citing Ex. 1055, 18:21–20:3; Ex. 1111 ¶ 98; Ex. 1169 ¶¶ 29–33).

Petitioner correctly notes that Patent Owner does not account for any patents[14] covering the insulin glargine compound. *See* Resp. 57–60; Ex. 1055, 18:–20:3 (Dr. Baker's testimony that he generally understands what "blocking patents" are, but did not investigate whether there was a blocking patent).

[14] Dr. Langer testifies that U.S. Patent No. 6,100, 376 ("the '376 patent") and U.S. Patent No. 5,656,722 ("the '722 patent") are both directed to "certain insulin analogs, including insulin glargine." Ex. 1111 ¶ 98 (citing Ex. 1171 ('376 patent); Ex. 1172 ('722 patent)). The '376 patent has an issue date of August 8, 2000, and expired on November 6, 2009. Ex. 1171 [45]; *see, e.g.*, Ex. 1088, 954 (Food & Drug Administration, *Approved Drugs with Therapeutic Equivalence Evaluations* (27th ed. 2007), also known as the "Orange Book," listing the '376 patent under the entry for "INSULIN GLARGINE RECOMBINANT; LANTUS" and noting that the '376 patent expires on November 6, 2009). The '722 patent has an issue date of August 12, 1997, and expired on September 12, 2014. Ex. 1172 [45]; *see, e.g.*, Ex. 1088, 954 (Orange Book listing the '722 patent under the entry for "INSULIN GLARGINE RECOMBINANT; LANTUS" and noting that the '722 patent expires on September 12, 2014).

Petitioner, on the other hand, offers testimony that at least two of Patent Owner's patents—the '722 patent and the '376 patent—"are considered to be blocking patents" and that other of Patent Owner's patents had been listed in the Orange Book as covering the Lantus product. Ex. 1169 ¶¶ 30, 32; Ex. 1111 ¶ 98 (citing Ex. 1171; Ex. 1172); *see also* Ex. 1088, 954 (Orange Book entry listing patents covering Lantus). Dr. McDuff testifies that the patents "would have blocked competitors from commercializing a product that embodied" the same technologies and "provided strong disincentives for others to develop and commercialize" the technology described in the '652 patent. Ex. 1169 ¶ 32. We credit Dr. McDuff's testimony and find, on the record before us, that Patent Owner's insulin glargine patents may have precluded others from entering the market with their own insulin glargine formulation products.

We find Patent Owner's evidence of commercial success weak in light of Patent Owner's blocking patents covering the insulin glargine compound—a required component of the pharmaceutical compositions claimed in the '652 patent. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1339 (Fed. Cir. 2018); *see Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) ("Where market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the claims], from evidence of commercial success, is weak."). Because Patent Owner could have precluded others from market entry prior to the patents covering insulin glargine expiring, Patent Owner's evidence of commercial success is insufficient to support the nonobviousness of the challenged claims.

4. Conclusion as to obviousness

Having considered the parties' arguments and evidence, we evaluate all of the evidence together to make a final determination of obviousness. *In re*

Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1075 (Fed. Cir. 2012) (stating that a fact finder must consider all evidence relating to obviousness before finding patent claims invalid). In so doing, we conclude that Petitioner has satisfied its burden of demonstrating, by a preponderance of the evidence, that: (1) claims 1–25 of the '652 patent would have been obvious over the combination Lantus Label and Lougheed; (2) claims 7 and 24 of the '652 patent would have been obvious over the combination of Lantus Label and FASS; (3) claims 7 and 24 of the '652 patent would have been obvious over the combination of Lantus Label and Grau; (4) claims 1–25 of the '652 patent would have been obvious over the combination Owens and Lougheed; (5) claims 7 and 24 of the '652 patent would have been obvious over the combination of Owens and FASS; and (6) claims 7 and 24 of the '652 patent would have been obvious over the combination of Owens and Grau.

IV. MOTIONS TO SEAL

Patent Owner and Petitioner each filed unopposed Motions to Seal portions of certain papers and exhibits. Papers 41, 45, 78, 87. Accompanying Petitioner's first motion is a request to enter an agreed upon protective order. Paper 41, Attachment.

Patent Owner seeks to seal Exhibits 1144–1161 and the portions of Petitioner's Reply (Paper 43) and Dr. Langer's declaration (Ex. 1111) that reference Exhibits 1144–1161 or the information contained in those exhibits. Paper 45 (Patent Owner's supplemental motion). Patent Owner also seeks to seal portions of Exhibits 2065–2068, and the portions of Patent Owner's sur-reply (Paper 79) that reference those exhibits. Paper 78. In support of its motions, Patent Owner asserts that the information it seeks to seal is highly confidential and

proprietary, that concrete harm would result upon its disclosure, there is a need to rely on the information they seek to seal, and that its interest in maintaining confidentiality outweigh the public interest in an open record. *See, e.g.*, Paper 45, 2–15.

Petitioner seeks to seal Exhibit 1086 and the portions of its sur-sur-reply (Paper 86) that reference Exhibits 2065–2068. Papers 41, 87. In support of its motion to seal Exhibit 1086 (diabetes-treatment market data), Petitioner asserts that the exhibit consists of "third-party proprietary commercial information that would lose [its] value if publicly available." Paper 41, 2–3. Petitioner also asserts that the Board has sealed similar information in other *inter partes* review proceedings, that having the data in the record permits the Board and Patent Owner to assess the basis of Dr. McDuff's opinions, and that the public interest is satisfied because the public can access Dr. McDuff's full expert declaration. *Id.* In support of its motion to seal portions of the sur-sur-reply, Petitioner notes that the sur-sur-reply references information from papers that Patent Owner has moved to seal. Paper 87, 1.

Petitioner did not oppose Patent Owner's motions, and Patent Owner did not oppose Petitioner's motions. Additionally, Patent Owner filed a public version of its sur-reply (Paper 80) and proposed redacted public versions of Petitioner's Reply and Dr. Langer's declaration (Paper 45, Attachments 1–2). Petitioner filed a public version of its sur-sur-reply. Paper 88.

"There is a strong public policy for making all information filed in a quasi-judicial administrative proceeding open to the public, especially in an *inter partes* review which determines the patentability of claims in an issued patent and therefore affects the rights of the public." *Garmin Int'l v. Cuozzo Speed Techs., LLC*, IPR2012–00001, slip op. at 1–2 (PTAB Mar. 14, 2013) (Paper 34). For this

reason, except as otherwise ordered, the record of an *inter partes* review trial shall be made available to the public. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. The standard for granting a motion to seal is good cause. 37 C.F.R. § 42.54. That standard includes a showing that "(1) the information sought to be sealed is truly confidential, (2) a concrete harm would result upon public disclosure, (3) there exists a genuine need to rely in the trial on the specific information sought to be sealed, and (4) on balance, an interest in maintaining confidentiality outweighs the strong public interest in having an open record." *Argentum Pharms. LLC v. Alcon Research, Ltd.*, Case IPR2017-01053, slip op. at 4 (Paper 27) (PTAB Jan. 19, 2018) (informative).

After having considered the submissions, we determine that the parties' proposed protective order, although not the Board's default order, is acceptable and will be entered. We also determine that there is good cause for granting the Motions with respect to all information, except the information in Petitioner's sur-sur-reply, as we explain further below. Specifically, the parties demonstrate that the information they seek to seal consists of confidential and proprietary research and development information, confidential packaging specifications, confidential regulatory submissions, and confidential commercial information. And we see little harm to the public's interest in restricting access to the information because we do not rely on any confidential information in this decision. We further note that the public versions of Petitioner's Reply, Dr. Langer's declaration, and Patent Owner's sur-reply appear to redact only that information that the parties seek to seal in their motions.[15]

[15] Patent Owner shall file its proposed public version of Petitioner's Reply as a paper in this proceeding and its proposed public version of Dr. Langer's declaration as an exhibit in this proceeding.

As to Petitioner's motion to seal the sur-sur-reply (Paper 87), other than noting that it references information from papers that Patent Owner moves to seal, Petitioner provides no justification for why the redacted portions of the sur-sur-reply should be kept confidential. Thus, Petitioner fails to satisfy the good cause requirement and we deny Petitioner's motion without prejudice to Patent Owner.

We authorize Patent Owner to file, with ten (10) business days of the date of this decision, a motion to seal portions of Petitioner's sur-sur-reply, setting forth a showing why the particular portions of those documents the parties seek to seal are confidential and that good cause exists to seal those portions. We instruct the parties to work together to prepare proposed redactions to Petitioner's sur-sur-reply. Any proposed redactions should be narrowly tailored. The parties shall meet and confer in good faith as necessary to comply with our orders in this decision. 37 C.F.R. § 42.11.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner establishes, by a preponderance of the evidence, that claims 1–25 of the '652 patent are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Strike (Paper 47) is denied-in-part and dismissed-in-part as moot;

FURTHER ORDERED that Petitioner's Motion to Exclude (Paper 57) is dismissed as moot;

FURTHER ORDERED that Patent Owner's Motion to Exclude (Paper 61) is denied-in-part and dismissed-in-part as moot;

FURTHER ORDERED that the parties' proposed protective order (Paper 41, Attachment) is entered and governs the treatment and filing of confidential information in this proceeding;

FURTHER ORDERED that Petitioner's first Motion to Seal (Paper 41) is granted;

FURTHER ORDERED that Petitioner's second Motion to Seal (Paper 87) is denied without prejudice;

FURTHER ORDERED that Patent Owner's Supplemental Motion to Seal (Paper 45) and Patent Owner's Motion to Seal (Paper 78) are granted;

FURTHER ORDERED that Patent Owner shall file its proposed public version of Petitioner's Reply as a paper in this proceeding and its proposed public version of Dr. Langer's declaration as an exhibit in this proceeding within five (5) business days of this decision;

FURTHER ORDERED that Patent Owner is authorized to file a motion to seal portions of Petitioner's sur-sur-reply (Paper 86), within ten (10) business days of this decision, and in accordance with the instructions set forth above; and

FURTHER ORDERED that this is a Final Written Decision; therefore, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2017-01526
Patent 7,476,652 B2

PETITIONER:

Jeffrey Guise
Richard Torczon
Douglas Carsten
Lorelei Westin
Clark Lin
Alina Litoshyk
Nicole W. Stafford
WILSON SONSINI GOODRICH & ROSATI
jguise@wsgr.com
rtorczon@wsgr.com
dcarsten@wsgr.com
lwestin@wsgr.com
clin@wsgr.com
nstafford@wsgr.com

PATENT OWNER:

Elizabeth Weiswasser
Anish Desai
Aaron Pereira
WEIL, GOTSHAL & MANGES LLP
elizabeth.weiswasser@weil.com
anish.desai@weil.com
aaron.pereira@weil.com

EXHIBIT 6

General Docket
United States Court of Appeals for the Federal Circuit

Court of Appeals Docket #: 19-1368 **Docketed:** 01/07/2019
Sanofi-Aventis Deutschland v. Mylan Pharmaceuticals Inc.
Appeal From: United States Patent and Trademark Office
Fee Status: fee paid

Case Type Information:
1) BCA or PTO
2) Patent Trial and Appeal Board
3) -

Originating Court Information:
District: PATO-1 : IPR2017-01526
Trial Judge: Michelle Nerozzi Ankenbrand, Administrative Patent Judge
Trial Judge: Erica A. Franklin, Administrative Patent Judge
Trial Judge: Robert A. Pollock, Administrative Patent Judge
Date Filed: 06/05/2017
Date NOA Filed: 01/04/2019
Date Rec'd COA: 01/04/2019

District: PATO-1 : IPR2017-01528
Date Filed: 06/05/2017

Prior Cases:
None

Current Cases:

	Lead	Member	Start	End
Consolidated	19-1368	19-1369	01/18/2019	

SANOFI-AVENTIS DEUTSCHLAND GMBH
Appellant

Elizabeth Weiswasser
Direct: 212-310-8022
Email: Elizabeth.Weiswasser@weil.com
[LD NTC Retained]
Weil, Gotshal & Manges LLP
767 Fifth Avenue
32nd Floor
New York, NY 10153

Adam Banks
Direct: 212-310-8419
Email: adam.banks@weil.com
[COR NTC Retained]
Weil, Gotshal & Manges LLP
767 Fifth Avenue
32nd Floor
New York, NY 10153

Anish R. Desai
Direct: 212-310-8730
Email: anish.desai@weil.com
[COR NTC Retained]
Weil, Gotshal & Manges LLP
767 Fifth Avenue
New York, NY 10153

Andrew Gesior, -
Direct: 212-310-8000
Email: Andrew.Gesior@weil.com
[COR NTC Retained]
Weil, Gotshal & Manges LLP
767 Fifth Avenue
New York, NY 10153

Aaron L. J. Pereira, Attorney

Direct: 212-310-8086
Email: aaron.pereira@weil.com
[COR NTC Retained]
Weil, Gotshal & Manges LLP
767 Fifth Avenue
New York, NY 10153

Robert T. Vlasis, III
Direct: 202-682-7024
Email: robert.vlasis@weil.com
[COR NTC Retained]
Weil, Gotshal & Manges LLP
Suite 600
2001 M Street NW
Suite 600
Washington, DC 20036

v.

MYLAN PHARMACEUTICALS INC.
Appellee

Douglas H. Carsten, Attorney
Direct: 858-350-2300
Email: dcarsten@wsgr.com
[LD NTC Retained]
Wilson, Sonsini, Goodrich & Rosati, PC
IP Patents & Innovations
Suite 200
12235 El Camino Real
San Diego, CA 92130

Adam William Burrowbridge
Direct: 202-973-8992
Email: aburrowbridge@wsgr.com
[COR NTC Retained]
Wilson, Sonsini, Goodrich & Rosati, PC
5th Floor
1700 K Street, NW
Washington, DC 20006

Wendy L. Devine, Attorney
Direct: 415-947-2027
Email: wdevine@wsgr.com
[COR NTC Retained]
Wilson, Sonsini, Goodrich & Rosati, PC
One Market Plaza
Spear Tower
Suite 3300
San Francisco, CA 94105

Lora Marie Green, Of Counsel
Direct: 301-461-9580
Email: lmgkofsky@gmail.com
[COR NTC Retained]
Wilson, Sonsini, Goodrich & Rosati, PC
Fifth Floor
1700 K Street, NW
Washington, DC 20006

Jeffrey William Guise, Attorney
Direct: 858-350-2300
Email: jguise@wsgr.com
[COR NTC Retained]
Wilson, Sonsini, Goodrich & Rosati, PC
IP Patents & Innovations
Suite 200
12235 El Camino Real
San Diego, CA 92130

Alina Leonidovna Litoshyk, Attorney
Direct: 858-350-2368

Email: alitoshyk@wsgr.com
[COR NTC Retained]
Wilson, Sonsini, Goodrich & Rosati, PC
IP Patents & Innovations
12235 El Camino Real
San Diego, CA 92130

Nicole W. Stafford, Attorney
Direct: 512-338-5402
Email: nstafford@wsgr.com
[COR NTC Retained]
Wilson, Sonsini, Goodrich & Rosati, PC
900 South Capital of Texas Highway
Las Cimas IV, Fifth Floor
Austin, TX 78746

Elham Firouzi Steiner, Esq.
Direct: 858-350-2246
Email: esteiner@wsgr.com
[COR NTC Retained]
Wilson, Sonsini, Goodrich & Rosati, PC
IP Patents & Innovations
Suite 200
12235 El Camino Real
San Diego, CA 92130

Richard Torczon, Attorney
Direct: 202-973-8811
Email: rtorczon@wsgr.com
[COR NTC Retained]
Wilson, Sonsini, Goodrich & Rosati, PC
1700 K Street, NW
Washington, DC 20006

Lorelei Westin, Esq., Attorney
Direct: 858-350-2225
Email: lwestin@wsgr.com
[COR NTC Retained]
Wilson, Sonsini, Goodrich & Rosati, PC
IP Patents & Innovations
Suite 200
12235 El Camino Real
San Diego, CA 92130

SANOFI-AVENTIS DEUTSCHLAND GMBH,

Appellant

v.

MYLAN PHARMACEUTICALS INC.,

Appellee

01/07/2019	☐ 1 57 pg, 294.95 KB	Appeal docketed. Received: 01/04/2019 [576160] Entry of Appearance due 01/22/2019. Certificate of Interest is due on 01/22/2019. Docketing Statement due 01/22/2019. Certified List due on 02/19/2019. [TAM] [Entered: 01/07/2019 09:58 AM]
01/16/2019	☐ 2 2 pg, 431.27 KB	Entry of appearance for Douglas H. Carsten as principal counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 01/16/2019 by email. [578615] [19-1368] This document is non-compliant. See Doc No. [6] [Richard Torczon] [Entered: 01/16/2019 02:53 PM]
01/16/2019	☐ 3 2 pg, 426.63 KB	Entry of appearance for Richard Torczon as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 01/16/2019 by email. [578617] [19-1368] This document is non-compliant. See Doc No. [6] [Richard Torczon] [Entered: 01/16/2019 02:55 PM]
01/16/2019	☐ 4 2 pg, 430.24 KB	Entry of appearance for Elham F. Steiner as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 01/16/2019 by email. [578622] [19-1368] This document is non-compliant. See Doc No. [6] [Richard Torczon] [Entered: 01/16/2019 02:58 PM]
01/16/2019	☐ 5 2 pg, 634.98 KB	Entry of appearance for Nicole W. Stafford as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 01/16/2019 by email. [578624] [19-1368] [Richard Torczon] [Entered: 01/16/2019 03:00 PM]
01/17/2019	☐ 6 2 pg, 67.56 KB	NOTICE OF NON-COMPLIANCE: The submissions of Appellee Mylan Pharmaceuticals Inc., Entry of Appearance for Elham Steiner, Richard Torczon, and Douglas Carsten [4], [3], [2], are not in compliance with the rules of this court (see attached). Compliant document due on 01/25/2019. Service as of this date by the Clerk of Court.[579075] [TAM] [Entered: 01/17/2019 03:48 PM]
01/18/2019	☐ 7 2 pg, 71.52 KB	ORDER consolidating appeals (19-1368 with 19-1369). Service as of this date by the Clerk of Court. [579224] [19-1368, 19-1369] [TAM] [Entered: 01/18/2019 09:05 AM]
01/18/2019	☐ 8	Note to file: The following cases are associated: 19-1368 (Lead) with 19-1369 (Member Case). FURTHER ENTRIES WILL BE ADDED TO THE LEAD APPEAL ONLY. [579225] [19-1368, 19-1369] [TAM] [Entered: 01/18/2019 09:15 AM]
01/18/2019	☐ 9 2 pg, 525.27 KB	Corrected Entry of appearance for Douglas H. Carsten as principal counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 01/18/2019 by email. [579250] [19-1368] [Richard Torczon] [Entered: 01/18/2019 10:39 AM]
01/18/2019	☐ 10 2 pg, 522.92 KB	Corrected Entry of appearance for Elham F. Steiner as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 01/18/2019 by email. [579252] [19-1368] [Richard Torczon] [Entered: 01/18/2019 10:41 AM]
01/18/2019	☐ 11 2 pg, 522.89 KB	Corrected Entry of appearance for Richard Torczon as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 01/18/2019 by email. [579255] [19-1368] [Richard Torczon] [Entered: 01/18/2019 10:43 AM]
01/18/2019	☐ 12 2 pg, 109.89 KB	Entry of appearance for Lorelei Westin as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 01/18/2019 by email. [579355] [19-1368] [Richard Torczon] [Entered: 01/18/2019 02:10 PM]
01/18/2019	☐ 13 2 pg, 755.67 KB	Entry of appearance for Jeffrey W. Guise as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 01/18/2019 by email. [579359] [19-1368] [Richard Torczon] [Entered: 01/18/2019 02:13 PM]
01/18/2019	☐ 14 2 pg, 310 KB	Entry of appearance for Alina Litoshyk as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 01/18/2019 by email. [579374] [19-1368] [Richard Torczon] [Entered: 01/18/2019 02:33 PM]
01/22/2019	☐ 15 2 pg, 116.3 KB	Entry of appearance for Elizabeth S. Weiswasser as principal counsel for Appellant Sanofi-Aventis Deutschland GmbH. Service: 01/21/2019 by email. [579501] [19-1368] [Elizabeth Weiswasser] [Entered: 01/21/2019 04:12 PM]
01/22/2019	☐ 16 2 pg, 124.54 KB	Entry of appearance for Anish R. Desai as of counsel for Appellant Sanofi-Aventis Deutschland GmbH. Service: 01/21/2019 by email. [579502] [19-1368] [Elizabeth Weiswasser] [Entered: 01/21/2019 04:14 PM]
01/22/2019	☐ 17 2 pg, 252.4 KB	Entry of appearance for Robert T. Vlasis as of counsel for Appellant Sanofi-Aventis Deutschland GmbH. Service: 01/21/2019 by email. [579503] [19-1368] [Elizabeth Weiswasser] [Entered: 01/21/2019 04:16 PM]
01/22/2019	☐ 18 2 pg, 109.73 KB	Entry of appearance for Aaron L. J. Pereira as of counsel for Appellant Sanofi-Aventis Deutschland GmbH. Service: 01/21/2019 by email. [579504] [19-1368] [Elizabeth Weiswasser] [Entered: 01/21/2019 04:18 PM]
01/22/2019	☐ 19 3 pg, 111.13 KB	Certificate of Interest for the Appellant Sanofi-Aventis Deutschland GmbH. Service: 01/21/2019 by email. [579505] [19-1368] [Elizabeth Weiswasser] [Entered: 01/21/2019 04:20 PM]
01/22/2019	☐ 20 4 pg, 105.67 KB	Docketing Statement for the Appellant Sanofi-Aventis Deutschland GmbH. Service: 01/21/2019 by email. [579506] [19-1368] [Elizabeth Weiswasser] [Entered: 01/21/2019 04:21 PM]
01/22/2019	☐ 21 2 pg, 286.28 KB	Certificate of Interest for the Appellee Mylan Pharmaceuticals Inc.. Service: 01/22/2019 by email. [579890] [19-1368] [Richard Torczon] [Entered: 01/22/2019 04:34 PM]
01/22/2019	☐ 22 4 pg, 87.93 KB	Docketing Statement for the Appellee Mylan Pharmaceuticals Inc.. Service: 01/22/2019 by email. [579891] [19-1368] [Richard Torczon] [Entered: 01/22/2019 04:35 PM]

02/27/2019	☐ 23 123 pg, 3.34 MB	Certified list from the United States Patent and Trademark Office. Service: 02/19/2019 by email. Appellant's brief is due 04/22/2019. [589040] [TAM] [Entered: 02/27/2019 12:07 PM]
03/28/2019	☐ 24 2 pg, 413.55 KB	Entry of appearance for Lora Green as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 03/28/2018 by email. [596270] [19-1368] [Richard Torczon] [Entered: 03/28/2019 02:36 PM]
03/29/2019	☐ 25 2 pg, 97.09 KB	Entry of appearance for Adam Burrowbridge as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 03/29/2019 by email. [596463] [19-1368] [Richard Torczon] [Entered: 03/29/2019 11:00 AM]
04/22/2019	☐ 26 2 pg, 88.63 KB	Entry of appearance for Adam B. Banks as of counsel for Appellant Sanofi-Aventis Deutschland GmbH. Service: 04/22/2019 by email. [602160] [19-1368] [Elizabeth Weiswasser] [Entered: 04/22/2019 09:56 PM]
04/22/2019	☐ 27 185 pg, 13.95 MB	FILED from Appellant Sanofi-Aventis Deutschland GmbH. Title: OPENING BRIEF. Service: 04/22/2019 by email. [602162] [19-1368] This document is non-compliant. See Doc No.[28] [Elizabeth Weiswasser] [Entered: 04/22/2019 10:06 PM]
04/25/2019	☐ 28 2 pg, 151.31 KB	NOTICE OF NON-COMPLIANCE: The submission of Appellant Sanofi-Aventis Deutschland GmbH, Opening Brief [27], is not in compliance with the rules of this court (see attached). Compliant document due on 05/02/2019. Appellee Mylan Pharmaceuticals Inc.'s brief is due 06/03/2019. Service as of this date by the Clerk of Court.[602933] [TAM] [Entered: 04/25/2019 01:52 PM]
04/25/2019	☐ 29 2 pg, 89.91 KB	Entry of appearance for Andrew Gesior as of counsel for Appellant Sanofi-Aventis Deutschland GmbH. Service: 04/25/2019 by email. [603005] [19-1368] [Elizabeth Weiswasser] [Entered: 04/25/2019 03:40 PM]
04/26/2019	☐ 30 183 pg, 10.8 MB	MODIFIED ENTRY: CORRECTED OPENING BRIEF FILED for Appellant Sanofi-Aventis Deutschland GmbH. Number of Pages: 52. Service: 04/26/2019 by email. [603404] --[Edited 05/01/2019 by TAM - compliance review complete] This brief has been corrected. See Doc No.[38] [Elizabeth Weiswasser] [Entered: 04/26/2019 05:01 PM]
05/28/2019	☐ 31 75 pg, 1.15 MB	MODIFIED ENTRY: RESPONSE BRIEF FILED for Appellee Mylan Pharmaceuticals Inc. Number of Pages: 62. Service: 05/28/2019 by email. Unless ordered otherwise, any responsive deadline runs from the date of service of this brief. See Fed. Cir. R. 31. [609947] --[Edited 05/31/2019 by TAM - compliance review complete] [Douglas Carsten] [Entered: 05/28/2019 08:17 PM]
06/18/2019	☐ 32 36 pg, 240.13 KB	MODIFIED ENTRY: REPLY BRIEF FILED for Appellant Sanofi-Aventis Deutschland GmbH. Number of Pages: 27. Service: 06/18/2019 by email. Unless ordered otherwise, any responsive deadline runs from the date of service of this brief. See Fed. Cir. R. 31. [615309] --[Edited 06/24/2019 by TAM - compliance review complete] [Elizabeth Weiswasser] [Entered: 06/18/2019 07:18 PM]
06/25/2019	☐ 33 518 pg, 95.65 MB	MODIFIED ENTRY: JOINT APPENDIX FILED for Sanofi-Aventis Deutschland GmbH. Number of Pages: 518. Service: 06/25/2019 by email. [616926] --[Edited 06/28/2019 by TAM - compliance review complete] [Elizabeth Weiswasser] [Entered: 06/25/2019 06:01 PM]
06/25/2019	☐ 34	MODIFIED ENTRY: CONFIDENTIAL JOINT APPENDIX FILED for Sanofi-Aventis Deutschland GmbH. Number of Pages: 558. Service: 06/25/2019 by email. [616927]--[Edited 06/28/2019 by TAM - compliance review complete] [Elizabeth Weiswasser] [Entered: 06/25/2019 06:12 PM]
06/27/2019	☐ 35 94 pg, 5.7 MB	MOTION of Appellee Mylan Pharmaceuticals Inc. to expedite hearing [Consent: opposed]. Service: 06/27/2019 by email. [617572] [19-1368] [Richard Torczon] [Entered: 06/27/2019 04:29 PM]
06/28/2019	☐ 36 2 pg, 66.51 KB	ORDER filed. Any opposition to the motion [35] shall be filed no later than July 8, 2019. Any reply in support of the motion is due no later than July 11, 2019. Service: 06/28/2019 by clerk. [617727] [NL] [Entered: 06/28/2019 11:11 AM]
06/28/2019	☐ 37 5 pg, 145.72 KB	Notice of Correction to the Brief Doc No. [30], Opening Brief Doc No. [30] for Appellant Sanofi-Aventis Deutschland GmbH. Service: 06/28/2019 by email. [617767] [19-1368] [Elizabeth Weiswasser] [Entered: 06/28/2019 12:34 PM]
06/28/2019	☐ 38 183 pg, 16.84 MB	MODIFIED ENTRY: CORRECTED OPENING BRIEF FILED for Appellant Sanofi-Aventis Deutschland GmbH. Number of Pages: 52. Service: 06/28/2019 by email. [617768]--[Edited 07/08/2019 by TAM - compliance review complete] [Elizabeth Weiswasser] [Entered: 06/28/2019 12:37 PM]
07/08/2019	☐ 39 39 pg, 767.82 KB	RESPONSE of Appellant Sanofi-Aventis Deutschland GmbH to the motion [35] filed by Appellee Mylan Pharmaceuticals Inc.. Service: 07/08/2019 by email. [619645] [19-1368] [Elizabeth Weiswasser] [Entered: 07/08/2019 06:35 PM]
07/11/2019	☐ 40 2 pg, 739.71 KB	Entry of appearance for Wendy L. Devine as of counsel for Appellee Mylan Pharmaceuticals Inc.. Service: 07/11/2019 by email. [620317] [19-1368] [Richard Torczon] [Entered: 07/11/2019 01:13 PM]
07/11/2019	☐ 41 13 pg, 171.26 KB	REPLY of Appellee Mylan Pharmaceuticals Inc. to response [39]. Service: 07/11/2019 by email. [620442] [19-1368] [Richard Torczon] [Entered: 07/11/2019 06:16 PM]
07/15/2019	☐ 42 2 pg, 72.35 KB	ORDER filed. The motion [35] is granted to the extent that the appeals will be placed on the September 2019 oral argument calendar. A copy of this order shall be transmitted to the merits panel assigned to

		these cases.; - *FOR CALENDAR*.. Service: 07/15/2019 by clerk. [621033] [NL] [Entered: 07/15/2019 02:51 PM]
07/16/2019	☐ 43	Outstanding paper copies of all briefs and appendices must be submitted within three business days from the date of issuance of this notice. See Fed. Cir. R. 25(c)(1). [621360] [TAM] [Entered: 07/16/2019 01:59 PM]
07/17/2019	☐ 44	6 paper copies of the Opening Response Brief [31] received from Appellee Mylan Pharmaceuticals Inc.. [621559] [CJF] [Entered: 07/17/2019 10:35 AM]
07/18/2019	☐ 45	6 paper copies of the Corrected Opening Brief [38] received from Appellant Sanofi-Aventis Deutschland GmbH. [622024] [CJF] [Entered: 07/18/2019 02:43 PM]
07/18/2019	☐ 46	6 paper copies of the Reply Brief [32] received from Appellant Sanofi-Aventis Deutschland GmbH. [622025] [CJF] [Entered: 07/18/2019 02:43 PM]
07/18/2019	☐ 47	6 paper copies of the Confidential Joint Appendix Brief [34] received from Appellant Sanofi-Aventis Deutschland GmbH. [622026] [CJF] [Entered: 07/18/2019 02:44 PM]
07/22/2019	☐ 48 2 pg, 146.44 KB	NOTICE OF ORAL ARGUMENT. Panel: 1909H. Case scheduled September 05, 2019 10:00 a.m. at the United States Court of Appeals for the Federal Circuit (Howard T. Markey National Courts Building, 717 Madison Place, NW Washington, DC 20439), Courtroom 402. Response to Notice of Oral Argument due: 08/15/2019. Please review the attached Notice. The response to notice of oral argument form can be found here. The Oral Argument Guide can be found here. [622592] [JAB] [Entered: 07/22/2019 03:23 PM]
08/15/2019	☐ 49 3 pg, 203.44 KB	Response to notice of oral argument from the Appellant Sanofi-Aventis Deutschland GmbH. [628494] [19-1368] [Elizabeth Weiswasser] [Entered: 08/15/2019 11:44 AM]
08/15/2019	☐ 50 3 pg, 200.17 KB	Response to notice of oral argument from the Appellee Mylan Pharmaceuticals Inc.. [628549] [19-1368] [Richard Torczon] [Entered: 08/15/2019 01:20 PM]
09/05/2019	☐ 51	Submitted after ORAL ARGUMENT by Adam Banks for Sanofi-Aventis Deutschland GmbH and Douglas H. Carsten for Mylan Pharmaceuticals Inc. Panel: Judge: Newman , Judge: Taranto , Judge: Chen. [633258] [JCP] [Entered: 09/05/2019 10:19 AM]
11/05/2019	☐ 52 23 pg, 855.2 KB	Citation of Supplemental Authority pursuant to Fed. R. App. P. 28(j) for Appellant Sanofi-Aventis Deutschland GmbH. Service: 11/05/2019 by email. [646907] [19-1368] [Elizabeth Weiswasser] [Entered: 11/05/2019 11:52 AM]
11/05/2019	☐ 53	Pursuant to Federal Rule of Appellate Procedure 44(a), the court certifies that a party questions the constitutionality of an Act of Congress. See entry [52]. [647097] [MJL] [Entered: 11/05/2019 04:57 PM]
11/06/2019	☐ 54 7 pg, 213.05 KB	MODIFIED ENTRY: RESPONSE of Appellee Mylan Pharmaceuticals Inc. to the supplemental authority [52] filed by Appellant Sanofi-Aventis Deutschland GmbH. Service: 11/06/2019 by email. [647249]--[Edited 11/06/2019 by JCA - Reason: to correct filing event] [Douglas Carsten] [Entered: 11/06/2019 11:17 AM]
11/06/2019	☐ 55 2 pg, 200.88 KB	Letter from Appellee Mylan Pharmaceuticals Inc. Update on status of co-pending district court trial. Service: 11/06/2019 by email. [647255] [19-1368] [Douglas Carsten] [Entered: 11/06/2019 11:22 AM]

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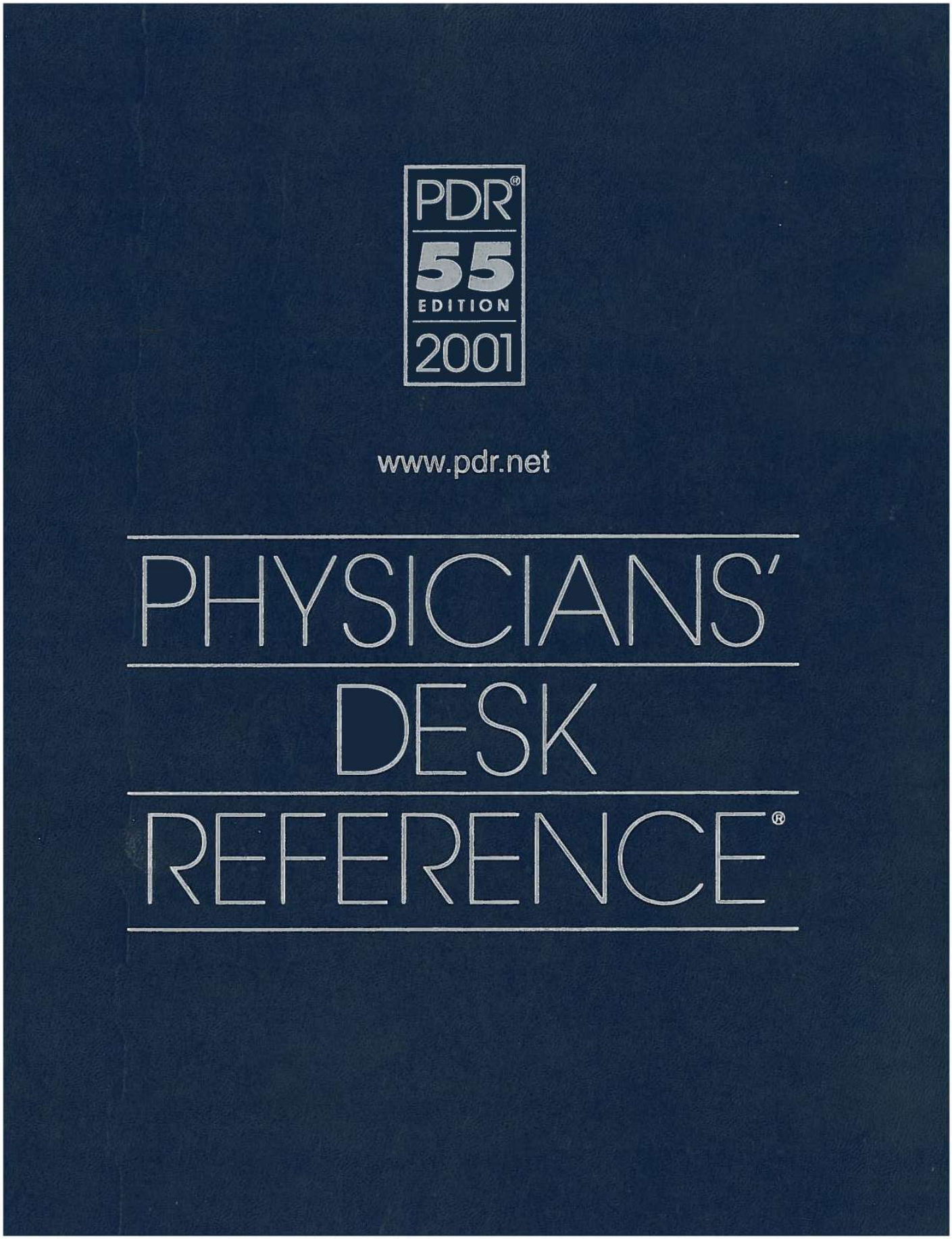
EXHIBIT 7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the outer gloves should be discarded into a biohazard waste container after use. A surgical instrument dedicated to the handling of the wafers should be used for wafer implantation. If repeat neurosurgical intervention is indicated, any wafer or wafer remnant should be handled as a potentially cytotoxic agent.

GLIADEL wafers should be handled with care. The aluminum foil laminate pouches containing GLIADEL should be delivered to the operating room and remain unopened until ready to implant the wafers. **The outside surface of the outer foil pouch is not sterile.**

Instructions for Opening Pouch Containing GLIADEL

Figure 1: To remove the sterile inner pouch from the outer pouch, locate the folded corner and slowly pull in an outward motion.

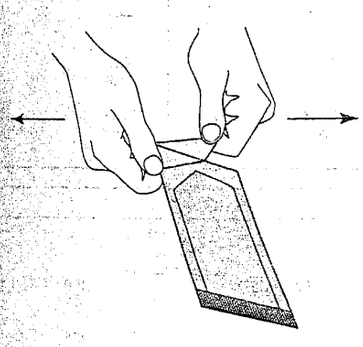


Figure 2: Do NOT pull in a downward motion rolling knuckles over the pouch. This may exert pressure on the wafer and cause it to break.

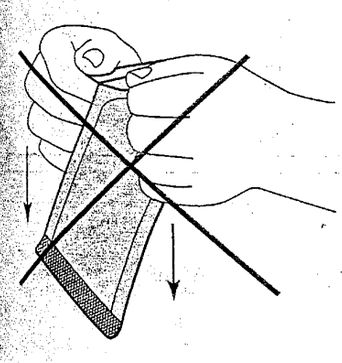


Figure 3: Remove the inner pouch by grabbing hold of the crimped edge and pulling upward.

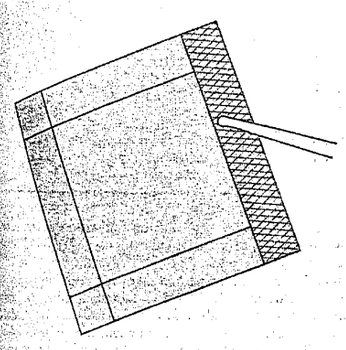


Figure 4: To open the inner pouch, gently hold the crimped edge and cut in an arc-like fashion around the wafer.

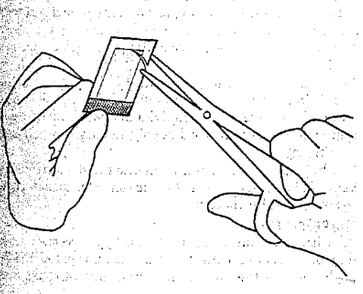
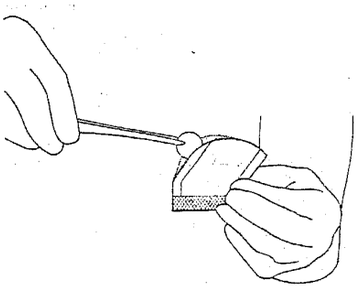


Figure 5: To remove the GLIADEL wafer, gently grasp the wafer with the aid of forceps and place it onto a designated sterile field.



Once the tumor is resected, tumor pathology is confirmed, and hemostasis is obtained, up to eight GLIADEL® Wafers (polifeprosan 20 with carmustine implant) may be placed to cover as much of the resection cavity as possible. Slight overlapping of the wafers is acceptable. Wafers broken in half may be used, but wafers broken in more than two pieces should be discarded in a biohazard container. Oxidized regenerated cellulose (Surgicel®) may be placed over the wafers to secure them against the cavity surface. After placement of the wafers, the resection cavity should be irrigated and the dura closed in a water tight fashion.

Unopened foil pouches may be kept at ambient room temperature for a maximum of six hours at a time.

HOW SUPPLIED

GLIADEL is available in a single dose treatment box containing eight individually pouched wafers. Each wafer contains 7.7 mg of carmustine and is packaged in two aluminum foil laminate pouches. The inner pouch is sterile and is designed to maintain product sterility and protect the product from moisture. The outer pouch is a peelable overwrap. **The outside surface of the outer pouch is not sterile.** GLIADEL must be stored at or below −20°C (−4°F).

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. JAMA, 1985; 253(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure — Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.
5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA — A Cancer Journal for Clinicians, 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm, 1990; 47:1033-1049.
7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm, 1986; 43:1193-1204.

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Shown in Product Identification Guide, page 307

LANTUS®

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[lăn' tus]

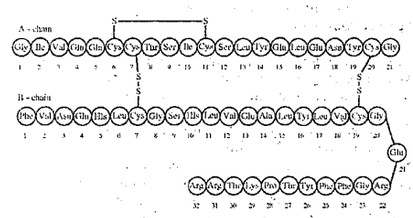
(insulin glargine [rDNA origin] injection)

Prescribing Information as of April 2000

LANTUS® must not be diluted or mixed with any other insulin or solution.

DESCRIPTION

LANTUS® (insulin glargine [rDNA origin] injection) is a sterile solution of insulin glargine for use as an injection. Insulin glargine is a recombinant human insulin analog that is a long-acting (up to 24-hour duration of action), parenteral blood-glucose-lowering agent. (See CLINICAL PHARMACOLOGY). LANTUS is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. Chemically, it is 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin and has the empirical formula $C_{267}H_{404}N_{72}O_{78}S_6$ and a molecular weight of 6063. It has the following structural formula:



LANTUS consists of insulin glargine dissolved in a clear aqueous fluid. Each milliliter of LANTUS (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide. LANTUS has a pH of approximately 4.

CLINICAL PHARMACOLOGY

Mechanism of Action

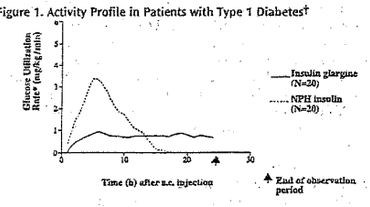
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

Pharmacodynamics

Insulin glargine is a human insulin analog that has been designed to have low aqueous solubility at neutral pH. At pH 4, as in the LANTUS injection solution, it is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak. This profile allows once-daily dosing as a patient's basal insulin.

In clinical studies, the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous insulin glargine is approximately the same as human insulin. In euglycemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than NPH human insulin. The effect profile of insulin glargine was relatively constant with no pronounced peak and the duration of its effect was prolonged compared to NPH human insulin. *Figure 1* shows results from a study in patients with type 1 diabetes conducted for a maximum of 24 hours after the injection. The median time between injection and the end of pharmacological effect was 14.5 hours (range: 9.5 to 19.3 hours) for NPH human insulin, and 24 hours (range: 10.8 to >24.0 hours) (24 hours was the end of the observation period) for insulin glargine.

Figure 1. Activity Profile in Patients with Type 1 Diabetes†



* Determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values); indicative of insulin activity.

† Between-patient variability (CV, coefficient of variation): insulin glargine, 84% and NPH, 78%.

The longer duration of action (up to 24 hours) of LANTUS is directly related to its slower rate of absorption and supports once-daily subcutaneous administration. The time course of action of insulins, including LANTUS, may vary between individuals and/or within the same individual.

Pharmacokinetics

Absorption and Bioavailability. After subcutaneous injection of insulin glargine in healthy subjects and in patients with diabetes, the insulin serum concentrations indicated a slower, more prolonged absorption and a relatively constant concentration/time profile over 24 hours with no pronounced peak in comparison to NPH human insulin. Serum insulin concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine.

After subcutaneous injection of 0.3 IU/kg insulin glargine in patients with type 1 diabetes, a relatively constant concentration/time profile has been demonstrated. The duration of action after abdominal, deltoid, or thigh subcutaneous administration was similar.

Metabolism. A metabolism study in humans indicates that insulin glargine is partly metabolized at the carboxyl terminus of the B chain in the subcutaneous depot to form two

Continued on next page

Lantus—Cont.

active metabolites with in vitro activity similar to that of insulin, M1 (21^{A}-Gly-insulin) and M2 (21^{A}-Gly-des-30^{B}-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

Special Populations

Age, Race, and Gender. Information on the effect of age, race, and gender on the pharmacokinetics of LANTUS is not available. However, in controlled clinical trials in adults (n=3890) and a controlled clinical trial in pediatric patients (n=349), subgroup analyses based on age, race, and gender did not show differences in safety and efficacy between insulin glargine and NPH human insulin.

Smoking. The effect of smoking on the pharmacokinetics/pharmacodynamics of LANTUS has not been studied.

Pregnancy. The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LANTUS has not been studied. (See PRECAUTIONS, Pregnancy)

Obesity. In controlled clinical trials, which included patients with Body Mass Index (BMI) up to and including 49.6 kg/m^2, subgroup analyses based on BMI did not show any differences in safety and efficacy between insulin glargine and NPH human insulin.

Renal Impairment. The effect of renal impairment on the pharmacokinetics of LANTUS has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin, including LANTUS, may be necessary in patients with renal dysfunction. (See PRECAUTIONS, Renal Impairment)

Hepatic Impairment. The effect of hepatic impairment on the pharmacokinetics of LANTUS has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including LANTUS, may be necessary in patients with hepatic dysfunction (See PRECAUTIONS, Hepatic Impairment)

CLINICAL STUDIES

The safety and effectiveness of insulin glargine given once-daily at bedtime was compared to that of once-daily and twice-daily NPH human insulin in open-label, randomized, active-control, parallel studies of 2327 adult patients and 349 pediatric patients with type 1 diabetes mellitus and 1563 adult patients with type 2 diabetes mellitus (see Tables 1–3). In general, LANTUS achieved a level of glycemic control similar to NPH human insulin as measured by glycated hemoglobin (GHb). The overall rate of hypoglycemia did not differ between patients with diabetes treated with LANTUS compared with NPH human insulin.

Type 1 Diabetes—Adult (see Table 1). In two large, randomized, controlled clinical studies (Studies A and B), patients with type 1 diabetes (Study A; n=585, Study B; n=534) were randomized to basal-bolus treatment with LANTUS once daily or to NPH human insulin once or twice daily and treated for 28 weeks. Regular human insulin was administered before each meal. LANTUS was administered at bedtime. NPH human insulin was administered once daily at bedtime or in the morning and at bedtime when used twice daily. In one large, randomized, controlled clinical study (Study C), patients with type 1 diabetes (n=619) were treated for 16 weeks with a basal-bolus insulin regimen where insulin lispro was used before each meal. LANTUS was administered once daily at bedtime and NPH human insulin was administered once or twice daily. In these studies, LANTUS and NPH human insulin had a similar effect on glycohemoglobin with a similar overall rate of hypoglycemia.

[See table 1 above]

Type 1 Diabetes—Pediatric (see Table 2). In a randomized, controlled clinical study (Study D), pediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. LANTUS was administered once daily at bedtime and NPH human insulin was administered once or twice daily. Similar effects on glycohemoglobin and the incidence of hypoglycemia were observed in both treatment groups.

[See table 2 above]

Type 2 Diabetes—Adult (see Table 3). In a large, randomized, controlled clinical study (Study E) (n=570), LANTUS was evaluated for 52 weeks as part of a regimen of combination therapy with insulin and oral antidiabetic agents (a sulfonylurea, metformin, acarbose, or combinations of these drugs). LANTUS administered once daily at bedtime was as effective as NPH human insulin administered once daily at bedtime in reducing glycohemoglobin and fasting glucose. There was a low rate of hypoglycemia that was similar in LANTUS and NPH human insulin treated patients. In a large, randomized, controlled clinical study (Study F), in patients with type 2 diabetes not using oral antidiabetic agents (n=518), a basal-bolus regimen of LANTUS once daily at bedtime or NPH human insulin administered once or twice daily was evaluated for 28 weeks. Regular human insulin was used before meals as needed. LANTUS had similar effectiveness as either once- or twice-daily NPH human insulin in reducing glycohemoglobin and fasting glucose with a similar incidence of hypoglycemia.

[See table 3 above]

Table 1: Type 1 Diabetes Mellitus—Adult

Treatment duration Treatment in combination with	Study A 28 weeks Regular insulin		Study B 28 weeks Regular insulin		Study C 16 weeks Insulin lispro	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Number of subjects treated	292	293	264	270	310	309
GHb						
Endstudy mean	8.13	8.07	7.55	7.49	7.53	7.60
Adj. mean change from baseline	+0.21	+0.10	−0.16	−0.21	−0.07	−0.08
LANTUS—NPH	+0.11		+0.05		+0.01	
95% CI for Treatment difference	(−0.03; +0.24)		(−0.08; +0.19)		(−0.11; +0.13)	
Basal insulin dose						
Endstudy mean	19.2	22.8	24.8	31.3	23.9	29.2
Mean change from baseline	−1.7	−0.3	−4.1	+1.8	−4.5	+0.9
Total insulin dose						
Endstudy mean	46.7	51.7	50.3	54.8	47.4	50.7
Mean change from baseline	−1.1	−0.1	+0.3	+3.7	−2.9	+0.3
Fasting blood glucose (mg/dL)						
Endstudy mean	146.3	150.8	147.8	154.4	144.4	161.3
Adj. mean change from baseline	−21.1	−16.0	−20.2	−16.9	−29.3	−11.9

Table 2: Type 1 Diabetes Mellitus—Pediatric

Treatment duration Treatment in combination with	Study D 28 weeks Regular insulin	
	LANTUS	NPH
Number of subjects treated	174	175
GHb		
Endstudy mean	8.91	9.18
Adj. mean change from baseline	+0.28	+0.27
LANTUS—NPH	+0.01	
95% CI for Treatment difference	(−0.24; +0.26)	
Basal insulin dose		
Endstudy mean	18.2	21.1
Mean change from baseline	−1.3	+2.4
Total insulin dose		
Endstudy mean	45.0	46.0
Mean change from baseline	+1.9	+3.4
Fasting blood glucose (mg/dL)		
Endstudy mean	171.9	182.7
Adj. mean change from baseline	−23.2	−12.2

Table 3: Type 2 Diabetes Mellitus—Adult

Treatment duration Treatment in combination with	Study E 52 weeks Oral agents		Study F 28 weeks Regular insulin	
	LANTUS	NPH	LANTUS	NPH
Number of subjects treated	289	281	259	259
GHb				
Endstudy mean	8.51	8.47	8.14	7.96
Adj. mean change from baseline	−0.46	−0.38	−0.41	−0.59
LANTUS—NPH	−0.08		+0.17	
95% CI for Treatment difference	(−0.28; +0.12)		(−0.00; +0.35)	
Basal insulin dose				
Endstudy mean	25.9	23.6	42.9	52.5
Mean change from baseline	+11.5	+9.0	−1.2	+7.0
Total insulin dose				
Endstudy mean	25.9	23.6	74.3	80.0
Mean change from baseline	+11.5	+9.0	+10.0	+13.1
Fasting blood glucose (mg/dL)				
Endstudy mean	126.9	129.4	141.5	144.5
Adj. mean change from baseline	−49.0	−46.3	−23.8	−21.6

INDICATIONS AND USAGE

LANTUS is indicated for once-daily subcutaneous administration at bedtime in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

CONTRAINDICATIONS

LANTUS is contraindicated in patients hypersensitive to insulin glargine or the excipients.

WARNINGS

Hypoglycemia is the most common adverse effect of insulin, including LANTUS. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

PRECAUTIONS

General

LANTUS is not intended for intravenous administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.

LANTUS must not be diluted or mixed with any other insulin or solution. If LANTUS is diluted or mixed, the solution may become cloudy, and the pharmacokinetic/pharmacodynamic profile (e.g., onset of action, time to peak effect) of LANTUS and/or the mixed insulin may be altered in an unpredictable manner. When LANTUS and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of LANTUS and regular human insulin. The relevance of these observations in dogs to humans is not known.

As with all insulin preparations, the time course of LANTUS action may vary in different individuals or at different times in the same individual and the rate of absorption is dependent on blood supply, temperature, and physical activity.

Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Hypoglycemia

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LANTUS. Hypoglycemia is the most common adverse effect of insulins.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. (See PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia. The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed. Patients being switched from twice daily NPH insulin to once-daily LANTUS should have their LANTUS dose reduced by 20% from the previous total daily NPH dose to reduce the risk of hypoglycemia. (See DOSAGE AND ADMINISTRATION, Changeover to LANTUS)

The prolonged effect of subcutaneous LANTUS may delay recovery from hypoglycemia.

In a clinical study, symptoms of hypoglycemia or counter-regulatory hormone responses were similar after intravenous insulin glargine and regular human insulin both in healthy subjects and patients with type 1 diabetes.

Renal Impairment

Although studies have not been performed in patients with diabetes and renal impairment, LANTUS requirements may be diminished because of reduced insulin metabolism, similar to observations found with other insulins. (See CLINICAL PHARMACOLOGY, Special Populations)

Hepatic Impairment

Although studies have not been performed in patients with diabetes and hepatic impairment, LANTUS requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins. (See CLINICAL PHARMACOLOGY, Special Populations)

Injection Site and Allergic Reactions

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Reports of injection site pain were more frequent with LANTUS than NPH human insulin (2.7% insulin glargine versus 0.7% NPH). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy.

Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalized skin reactions, angioedema, bronchospasm, hypotension, or shock and may be life threatening.

Intercurrent Conditions

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

Information for Patients

LANTUS must only be used if the solution is clear and colorless with no particles visible. (See DOSAGE AND ADMINISTRATION, Preparation and Handling)

Patients must be advised that LANTUS must not be diluted or mixed with any other insulin or solution. (See PRECAUTIONS, General)

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycemia and hyperglycemia management.

Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LANTUS Information for the Patient circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia.

Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy.

Drug Interactions

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which is for the rat approximately 10 times and for the mouse approximately 5 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m^2. The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m^2, maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH human insulin.

Pregnancy

Teratogenic Effects: Pregnancy Category C. Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. The drug was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m^2. In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m^2, were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of insulin glargine in pregnant women. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is unknown whether insulin glargine is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when LANTUS is administered to a nursing woman. Lactating women may require adjustments in insulin dose and diet.

Pediatric Use

Safety and effectiveness of LANTUS have been established in the age group 6 to 15 years with type 1 diabetes.

Geriatric Use

In controlled clinical studies comparing insulin glargine to NPH human insulin, 593 of 3890 patients with type 1 and type 2 diabetes were 65 years and older. The only difference in safety or effectiveness in this subpopulation compared to the entire study population was an expected higher incidence of cardiovascular events in both insulin glargine and NPH human insulin-treated patients.

In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly. (See PRECAUTIONS, Hypoglycemia)

ADVERSE REACTIONS

The adverse events commonly associated with LANTUS include the following:

Body as a whole: allergic reactions (See PRECAUTIONS)

Skin and appendages: injection site reaction, lipodystrophy, pruritus, rash (See PRECAUTIONS)

Other: hypoglycemia (See WARNINGS and PRECAUTIONS)

In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy. Other treatment-emergent injection site reactions occurred at similar incidences with both insulin glargine and NPH human insulin.

Retinopathy was evaluated in the clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH treatment groups were similar for patients with type 1 and type 2 diabetes. Progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). In one clinical study involving patients with type 2 diabetes, a difference in the number of subjects with ≥3-step progression in ETDRS scale over a 6-month period was noted by fundus photography (7.5% in LANTUS group versus 2.7% in NPH treated group). The overall relevance of this isolated finding cannot be determined due to the small number of patients involved, the short follow-up period, and the fact that this finding was not observed in other clinical studies.

OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes long-term and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia.

DOSAGE AND ADMINISTRATION

LANTUS is a recombinant human insulin analog. Its potency is approximately the same as human insulin. It exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-daily dosing.

LANTUS should be administered subcutaneously once a day at bedtime. LANTUS is not intended for intravenous administration (See PRECAUTIONS). Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. The desired blood glucose levels as well as the doses and timing of antidiabetic medications must be determined individually. Blood glucose monitoring is recommended for all patients with diabetes. The prolonged duration of activity of LANTUS is dependent on injection into subcutaneous space.

As with all insulins, injection sites within an injection area (abdomen, thigh or deltoid) must be rotated from one injection to the next.

In clinical studies, there was no relevant difference in insulin glargine absorption after abdominal, deltoid, or thigh subcutaneous administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

LANTUS is not the insulin of choice for the treatment of diabetic ketoacidosis. Intravenous short-acting insulin is the preferred treatment.

Pediatric Use

LANTUS can be safely administered to pediatric patients ≥6 years of age. Administration to pediatric patients <6 years has not been studied. Based on the results of a study in pediatric patients, the dose recommendation for changeover to LANTUS is the same as described for adults in DOSAGE AND ADMINISTRATION, Changeover to LANTUS.

Initiation of LANTUS Therapy

In a clinical study with insulin naïve patients with type 2 diabetes already treated with oral antidiabetic drugs, LANTUS was started at an average dose of 10 IU once daily, and subsequently adjusted according to the patient's need to a total daily dose ranging from 2 to 100 IU.

Changeover to LANTUS

If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with LANTUS, the amount and timing of short-acting insulin or fast-acting insulin analog or the dose of any oral antidiabetic drug may need to be adjusted. In clinical studies, when patients were transferred from once-daily NPH human insulin or ultralente human insulin to once-daily LANTUS, the initial dose was usually not changed. However, when patients were transferred from twice-daily NPH human insulin to LANTUS once daily at bedtime, to reduce the risk of hypoglycemia, the initial dose (IU) was usually reduced by approximately 20% (compared to total daily IU of NPH human insulin) within the first week of treatment and then adjusted based on patient response. (See PRECAUTIONS, Hypoglycemia)

A program of close metabolic monitoring under medical supervision is recommended during transfer and in the initial weeks thereafter. The amount and timing of short-acting insulin or fast-acting insulin analog may need to be adjusted. This is particularly true for patients with acquired antibodies to human insulin needing high-insulin doses and occurs with all insulin analogs. Dose adjustment of LANTUS and other insulins or oral antidiabetic drugs may be required; for example, if the patient's weight or lifestyle changes or other circumstances arise that increase susceptibility to hypoglycemia or hyperglycemia. (See PRECAUTIONS, Hypoglycemia)

The dose may also have to be adjusted during intercurrent illness. (See PRECAUTIONS, Intercurrent Conditions)

Preparation and Handling

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. LANTUS must only be used if the solution is clear and colorless with no particles visible.

The syringes must not contain any other medicinal product or residue.

Mixing and diluting. LANTUS must not be diluted or mixed with any other insulin or solution. (See PRECAUTIONS, General)

Cartridge version only: If the OptiPen™ One Insulin Delivery Device malfunctions, LANTUS may be drawn from the cartridge into a U 100 syringe and injected.

Continued on next page

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HOW SUPPLIED

LANTUS 100 units per mL (U 100) is available in the following package sizes:
5 mL vials (NDC 0088-2220-32)
10 mL vials (NDC 0088-2220-33)
3 mL cartridges*, package of 5 (NDC 0088-2220-52)
*Cartridges are for use only in the OptiPen™ One Insulin Delivery Device

Storage

Unopened LANTUS vials and cartridges should be stored in a refrigerator, 36°F - 46°F (2°C - 8°C). LANTUS should not be stored in the freezer and it should not be allowed to freeze.
If refrigeration is not possible, the 10 mL vial or cartridge of LANTUS in use can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 86°F (30°C). Unrefrigerated 10 mL vials and cartridges must be used within the 28-day period or they must be discarded.
If refrigeration is not possible, 5 mL vials of LANTUS in use can be kept unrefrigerated for up to 14 days away from direct heat and light, as long as the temperature is not greater than 86°F (30°C). Unrefrigerated 5 mL vials must be used within the 14-day period or they must be discarded.
If refrigerated, the 5 mL vial of LANTUS in use can be kept for up to 28 days. Once the cartridge is placed in an OptiPen One, it should not be put in the refrigerator.
Rx only
Prescribing Information as of April 2000
Manufactured by:
Hoechst Marion Roussel Deutschland GmbH
D-65926 Frankfurt am Main
Germany
Manufactured for:
Aventis Pharmaceuticals Inc.
Kansas City, MO 64137 USA
US Patents 5,656,722, 5,370,629, and 5,509,905
Made in Germany
www.aventispharma-us.com

LANTUS®
(insulin glargine [Recombinant DNA origin] injection)

Patient Information for the LANTUS Vial

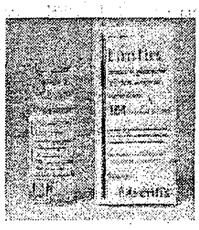
This leaflet tells you about LANTUS (LAN-tus) and about how to use LANTUS in a vial. At the end of the leaflet is a list of vocabulary words you may find useful. Read this information carefully before you use LANTUS. Read the information you get when you refill your LANTUS prescriptions because there may be new information. This leaflet does not take the place of complete discussions with your health care professional. If you have questions about LANTUS or about diabetes, talk with your health care professional.

What is the most important information I should know about LANTUS?

Do not dilute or mix LANTUS with any other insulin or solution. It will not work as intended, and you may lose blood sugar control, which could be serious.

What is LANTUS?

LANTUS is a long-acting synthetic (man-made) human insulin to treat diabetes. You need a prescription to get LANTUS. Always be sure the pharmacy gives you the right insulin. The carton and vial should look like the ones in this picture.



Diabetes is a disease caused when the body cannot produce or use insulin. Insulin is a hormone produced by the pancreas. Your body needs insulin to turn glucose (sugar) from food into energy. If your body does not make enough insulin, you need another source of insulin so you will not have too much sugar in your blood. That is why you must take insulin injections.
LANTUS is similar to the insulin made by your body. It is used once a day to lower blood glucose. Like other insulins, you take LANTUS by injecting it in the fatty layer under the skin (subcutaneously). The dose your health care professional prescribes helps keep the glucose level in your blood close to normal.
You will be able to tell if LANTUS is working by testing your blood and/or urine for glucose.
LANTUS contains active and inactive ingredients. The active ingredient is insulin. It is dissolved in a colorless sterile (germ-free) fluid. The concentration is 100 units/mL (U-100). Inactive ingredients are zinc, glycerol, m-cresol, and water for injection.
Insulin injections play an important role in keeping your diabetes in control. But the way you live—your diet, careful monitoring of your glucose levels, exercise, and planned physical activity—all work with your insulin to help you control your diabetes.

Who should not take LANTUS?

You should not take LANTUS if you are allergic to insulin or any of the inactive ingredients in LANTUS.

How should I take LANTUS?

Inject LANTUS under your skin once a day at bedtime. You do not need to shake the vial before use. You should look at the medicine in the vial. If the medicine is cloudy or has particles in it, throw the vial away and get a new one.

What sort of syringe should I use?

Always use a syringe that is marked for U-100 insulin preparations. If you use the wrong syringe, you may get the wrong dose and develop a blood glucose level that is too low or too high.
Use disposable syringes and needles only once. Throw them away properly. Use a new needle and syringe every time you dose. **Never** share needles and syringes.

How do I draw insulin into the syringe?

Do not dilute or mix LANTUS with any other insulin or solution. The syringe must not contain any other medicine or residue.

Follow these steps:

1. Wash your hands.
2. Check the insulin to make sure it is clear and colorless. Do not use it if it is cloudy or if you see particles.
3. If you are using a new vial, remove the protective cap. **Do not** remove the stopper.
4. Wipe the top of the vial with an alcohol swab.
5. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the vial and push the plunger to inject the air into the vial.
6. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand.
7. Make sure the tip of the needle is in the insulin. With your free hand, pull the plunger to withdraw the correct dose into the syringe.
8. Before you take the needle out of the vial, check the syringe for air bubbles. If bubbles are in the medicine, hold the syringe straight up and tap the side of the syringe until the bubbles float to the top. Push the bubbles out with the plunger and draw the insulin back in until you have the correct dose.
9. Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

How do I inject LANTUS?

Do not mix or dilute LANTUS with any other insulin or solution or LANTUS will not work as intended, and you may lose blood sugar control, which could be serious. You do not have to shake the vial before use.

Follow these steps:

1. Decide on an injection area—either upper arm, thigh, or abdomen. Injection sites within an injection area must be different from one injection to the next.
2. Use alcohol to clean the skin where you are going to inject.
3. Pinch the skin and hold it. Stick the needle in the way your doctor, nurse, or diabetes educator showed you.
4. Slowly push in the plunger of the syringe all the way, making sure you have injected all the insulin. Leave the needle in the skin for several seconds.
5. Pull the needle straight out and gently press on the spot where you injected yourself for several seconds. **Do not rub the area.**
6. Follow your health care professional's instructions for throwing away the needle and syringe.

If your blood glucose reading is high or low, or if your urine tests show glucose, tell your health care professional so the dose can be adjusted.

What can affect how much insulin I need?

Illness. Illness may change how much insulin you need. It is a good idea to think ahead and make a "sick day" plan with your health care professional so you will be ready when this happens. Be sure to test your blood and urine often and call your health care professional if you are sick.
Pregnancy and nursing. If you are pregnant or nursing, or if you plan to get pregnant, talk with your health care professional before you take LANTUS. Your diabetes may be harder to control when you are pregnant.
It is important for you to monitor your glucose closer than usual during this time.
Medicines. Other medicines can change the way insulin works. Therefore, tell your health care professional about all other medicines you are taking. Your insulin dosage may need to be changed by your health care professional. Do not change your medicine doses yourself.
For example, your body may need more insulin if you take birth control, thyroid, decongestant, or diet pills. Your body may need less insulin if you are taking antidepressants, antidiabetic pills, or ACE inhibitors (used to lower blood pressure and for certain heart conditions).
Exercise. Exercise may change the way your body uses insulin. Be sure to check with your health care professional before you start an exercise program.
Travel. If you travel across time zones, talk with your health care professional about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

What if I want to drink alcohol?

Before you drink alcohol, talk to your health care professional about its effect on diabetes.

What are the possible side effects of insulins?

1. Allergic reactions:
In rare cases, a patient may be allergic to an insulin product. Severe insulin allergies may be life-threatening. If you think you are having an allergic reaction, get medical help right away. Signs of insulin allergy are:
- a rash all over your body
- shortness of breath
- wheezing (trouble breathing)
- a fast pulse
- sweating
- low blood pressure

2. Hypoglycemia:
Hypoglycemia is often called an "insulin reaction" or "low blood sugar." It may occur when you do not have enough glucose in your blood. Common causes of hypoglycemia are illness, emotional or physical stress, too much insulin, too little food or missed meals, and too much exercise.
Some of the symptoms of hypoglycemia are:
- sudden cold sweat
- feeling shaky or nervous
- feeling very tired
- feeling sick to your stomach
- feeling dizzy
- blurry vision
- headache
- confusion
- personality changes

Early warning signs of hypoglycemia may be different or less noticeable in some people. That is why it is important to check your glucose as you have been advised by your doctor.
If you have hypoglycemia, your body needs sugar. That is why you should carry sugar, candy mints, or glucose tablets with you. Learn to recognize the signs and eat or drink something that has some sugar in it.
Hypoglycemia can be very dangerous. Severe hypoglycemia can cause confusion, seizures, and loss of consciousness. Someone with hypoglycemia who cannot take sugar by mouth needs medical help fast. Without immediate medical help, serious reactions or even death could occur.
You will have mild hypoglycemia once in a while when a meal is delayed, if you get sick, or if you are late with your insulin injection. But if hypoglycemia happens often or is severe, tell your health care professional about it. Also, if you have trouble recognizing the symptoms of hypoglycemia, talk with your health care professional.

3. Hyperglycemia:
Hyperglycemia occurs when you have too much glucose in your blood. Usually, it means there is not enough insulin to break down the food you eat into energy your body can use. Hyperglycemia can be caused by a fever, an infection, stress, eating more than you should, taking less insulin than prescribed, or it can be part of the natural progression of diabetes. Routine testing of your blood or urine will let you know if you have hyperglycemia. If your tests are often high, tell your health care professional so your dose of medicine can be changed.
If your glucose is often high, you can develop a very serious condition called diabetic ketoacidosis. Ketoacidosis can be life-threatening. If your blood tests show high amounts of glucose or your urine tests show high amounts of glucose or acetone, or if you have signs of ketoacidosis, you need to get medical help quickly. **Do not use LANTUS to treat diabetic ketoacidosis.** Signs of ketoacidosis are:
- sleepiness
- flushed (red) face
- thirst
- loss of appetite
- fruity odor on your breath

Signs of **severe** ketoacidosis are:
- heavy breathing
- fast pulse

4. Possible reactions on the skin at the injection site:
Injecting insulin can cause the following reactions on the skin at the injection site:
- a little depression in the skin (lipoatrophy)
- skin thickening (lipohypertrophy)
- red, swelling, itchy skin (injection site reaction)

An injection site reaction should clear up in a few days or a few weeks. If it does not go away and it continues to occur, tell your health care professional.
You can reduce the chance of getting lipoatrophy and lipohypertrophy if you change the injection site each time. Tell your health care professional if you have these problems. You may need to learn to inject your insulin a different way.

How should I store LANTUS?

Store new LANTUS vials in the refrigerator (not the freezer) between 36°F - 46°F (2°C - 8°C). Do not freeze LANTUS. If a vial freezes, throw it away.
Once a vial is opened, you can keep it in the refrigerator or as cool as possible (below 86°F [30°C]). The 10 mL vial is good for 28 days. The 5 mL vial is good for 14 days if stored in a cool place (below 86°F [30°C]) or 28 days if refrigerated. Keep LANTUS out of direct heat and light. For example, do not leave it in your car on a summer day.

VOCABULARY

Glucose—A form of sugar that the body uses for fuel. It is made when food is broken down in the digestive system. Blood carries glucose to the cells.
Hypoglycemia—Also called insulin reaction. It means that glucose levels in the blood are too low.
Hyperglycemia—Too much glucose in the blood. Usually testing, not symptoms, reveals a too-high level.
Insulin—A hormone that helps the cells in your body use glucose.

LANTUS—A long-acting insulin similar to insulin made by your body. It is used once a day at bedtime to lower blood glucose.
Lipoatrophy (LIP-o-AT-troe-fee)—Loss of fat under the skin. Can be caused by repeated insulin injections in the same place.
Lipohypertrophy (LIP-o-hi-PER-troe-fee)—A lump under the skin caused by an overgrowth of fat cells. Can be caused by repeated insulin injections in the same place.
Ketoacidosis (kee-toe-as-ih-DOE-sis)—A dangerous condition caused when the body does not have enough insulin.
Pancreas (PAN-kree-as)—A gland near the stomach that produces insulin.
Subcutaneous (sub-ku-TAE-nee-us)—The fatty layer under the skin.

ADDITIONAL INFORMATION

DIABETES FORECAST is a national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association, National Service Center, 1701 N. Beauregard Street, Alexandria, Virginia 22311, 1-800-DIABETES (1-800-342-2383).
Another publication, **DIABETES COUNTDOWN**, is available from the Juvenile Diabetes Foundation International (JDF), 120 Wall Street, 19th Floor, New York, New York 10005, 1-800-JDF-CURE (1-800-533-2873). You may also visit the JDF website at www.jdf.org.
To get more information about diabetes, check with your doctor or diabetes educator. To get more information about LANTUS, ask your health care professional or call 1-800-552-3656.
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LOVENOX® ℞
(enoxaparin sodium)
Injection

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.
The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.
Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.
The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also **WARNINGS, Hemorrhage**, and **PRECAUTIONS, Drug Interactions**).

DESCRIPTION

Lovenox Injection is a sterile solution containing enoxaparin sodium, a low molecular weight heparin. It is available in: prefilled syringes (30 and 40 mg), graduated prefilled syringes (60, 80, and 100 mg), and ampules (30 mg). Each dosage unit contains 10 mg enoxaparin sodium per 0.1 mL Water for Injection. The solution is preservative-free and intended for use only as a single-dose injection. (See **DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** for dosage unit descriptions.)
The pH of the injection is 5.5 to 7.5, with an approximate anti-Factor Xa activity per dosage unit of 1000 IU per every 10 mg of enoxaparin sodium (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard). Nitrogen is used in the headspace to inhibit oxidation.
Enoxaparin is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. The substance is the sodium salt. The average molecular weight is about 4500 daltons. The molecular weight distribution is:

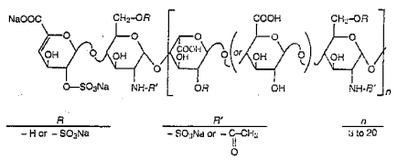
<2000 daltons	≤20%
2000 to 8000 daltons	≥68%
>8000 daltons	≤15%

STRUCTURAL FORMULA

[See chemical structure at top of next column]

CLINICAL PHARMACOLOGY

Enoxaparin is a low molecular weight heparin which has antithrombotic properties. In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously (SC) is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean±SD, 14.0±3.1) (based on areas under anti-Factor activity versus time curves) compared to the ratios observed for heparin (mean±SD, 1.22±0.13). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1 mg/kg dose, administered SC every 12 hours to patients in a large clinical trial resulted in aPTT values of 45 seconds or less in the majority of patients (n = 1607).



Pharmacodynamics: Maximum anti-Factor Xa and antithrombin (anti-Factor IIa) activities occur 3 to 5 hours after SC injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 µg/mL) and 0.38 IU/mL (3.83 µg/mL) after the 20 mg and the 40 mg clinically tested SC doses, respectively. Mean (n = 46) peak anti-Factor Xa activity was 1.1 IU/mL at steady state in patients with unstable angina receiving 1.0 mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, given SC, based on anti-Factor Xa activity is 92% in healthy volunteers. The volume of distribution of anti-Factor Xa activity is about 6 L. Following intravenous (i.v.) dosing, the total body clearance of enoxaparin is 26 mL/min. After i.v. dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc, 40% of radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after SC administration. Following a 40 mg SC once a day dose, significant anti-Factor Xa activity persists in plasma for about 12 hours.
Following SC dosing, the apparent clearance (CL/F) of enoxaparin is approximately 15 mL/min. Apparent clearance and A_{max} derived from anti-Factor Xa values following single SC dosing (40 mg and 60 mg) were slightly higher in males than in females. The source of the gender difference in these parameters has not been conclusively identified, however, body weight may be a contributing factor.
Apparent clearance and A_{max} derived from anti-Factor Xa values following single and multiple SC dosing in elderly subjects were close to those observed in young subjects. Following once a day SC dosing of 40 mg enoxaparin, the Day 10 mean area under anti-Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value. In subjects with moderate renal impairment (creatinine clearance 30 to 80 mL/min), anti-Factor Xa CL/F values were similar to those in healthy subjects. However, mean CL/F values of subjects with severe renal impairment (creatinine clearance <30 mL/min), were approximately 30% lower than the mean CL/F value of control group subjects. (See **PRECAUTIONS**.)

CLINICAL TRIALS

Hip or Knee Replacement Surgery: Lovenox Injection has been shown to prevent post-operative deep vein thrombosis (DVT) following hip or knee replacement surgery.
In a double-blind study, Lovenox Injection 30 mg every 12 hours SC was compared to placebo in patients with hip replacement. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued for 10 to 14 days after surgery. The data are provided below.

Efficacy of Lovenox Injection in Hip Replacement Surgery

Indication	Lovenox Dosing Regimen: 10 mg q.d. SC n (%)	30 mg q12h SC n (%)	40 mg q.d. SC n (%)
All Treated Hip Replacement Patients	161 (100)	208 (100)	199 (100)
Treatment Failures Total DVT (%)	40 (25)	22 (11)[1]	27 (14)
Proximal DVT (%)	17 (11)	8 (4)[2]	9 (5)

[1]p value versus Lovenox 10 mg once a day = 0.0008
[2]p value versus Lovenox 10 mg once a day = 0.0168

Efficacy of Lovenox Injection with Extended Prophylaxis Following Hip Replacement Surgery

Indication (Post-Discharge)	Post-Discharge Dosing Regimen: Lovenox 40 mg q.d. SC n (%)	Placebo q.d. SC n (%)
All Treated Extended Prophylaxis Patients	90 (100)	89 (100)
Treatment Failures Total DVT (%)	6 (7)[1] (95% CI: 3 to 14)	18 (20) (95% CI: 12 to 30)
Proximal DVT (%)	5 (6)[2] (95% CI: 2 to 13)	7 (8) (95% CI: 3 to 16)

[1]p value versus placebo = 0.008
[2]p value versus placebo = 0.537

Efficacy of Lovenox Injection in Hip Replacement Surgery

Indication	Dosing Regimen: Lovenox 30 mg q12h SC n (%)	Placebo q12h SC n (%)
All Treated Hip Replacement Patients	50 (100)	50 (100)
Treatment Failures Total DVT (%)	5 (10)[1]	23 (46)
Proximal DVT (%)	1 (2)[2]	11 (22)

[1]p value versus placebo = 0.0002
[2]p value versus placebo = 0.0134

A double-blind, multicenter study compared three dosing regimens of Lovenox Injection in patients with hip replacement. Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The data are provided below.
[See first table above]
There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimens.
Extended Prophylaxis in Hip Replacement Surgery: In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with enoxaparin 40 mg SC, initiated up to 12 hours prior to surgery for the prevention of post-operative deep vein thrombosis. At the end of the peri-operative period, all patients underwent bilateral venography. In a double-blind design, those patients with no venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin 40 mg (n = 90) once a day SC or to placebo (n = 89) for 3 weeks. In this population of patients, the incidence of deep vein thrombosis during extended prophylaxis was significantly lower for enoxaparin compared to placebo. The data are provided below.
[See second table above]
In a second study, patients undergoing hip replacement surgery were treated, while hospitalized, with enoxaparin 40 mg SC, initiated up to 12 hours prior to surgery. All patients were examined for clinical signs and symptoms of venous thromboembolic disease. In a double-blind design, patients without clinical signs and symptoms of venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin 40 mg (n = 131) once a day SC or to placebo (n = 131) for 3 weeks. Similar to the first study the incidence of deep vein thrombosis during extended prophylaxis was significantly lower for enoxaparin compared to placebo, with a statistically significant difference in both total DVT (enoxaparin 21 [16%] versus placebo 45 [34%]; p = 0.001) and proximal DVT (enoxaparin 8 [6%] versus placebo 28 [21%]; p = <0.001).
In a double-blind study, Lovenox Injection 30 mg every 12 hours SC was compared to placebo in 99 patients undergoing knee replacement surgery. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued up to 15 days after surgery. The incidence of proximal and total deep vein thrombosis after surgery was significantly lower for enoxaparin compared to placebo. The data are provided below.

Continued on next page